Universitat de Lleida

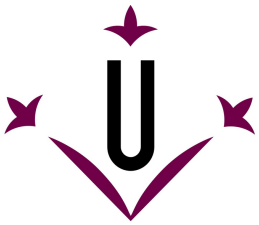
Patología ocular y el síndrome de apnea-hipoapnea del sueño

Mª Jesús Muniesa Royo

Dipòsit Legal: L.151-2015
http://hdl.handle.net/10803/285492

PATOLOGÍA OCULAR Y EL SÍNDROME DE APNEA–HIPOAPNEA DEL SUEÑO

Mª JESÚS MUNIESA ROYO



Universitat de Lleida

DIRECTORES

Dr. FERRÁN BARBÉ

Dr. VALENTÍN HUERVA

TUTORA

Dra.CARMEN JURJO

Septiembre 2014

MªJesús Muniesa Royo: *Patología Ocular y el Síndrome de Apnea-Hipoapnea del Sueño,* Septiembre 2014.

U N I V E R S I T A T D E L L E I D A

Departament de Cirurgia

C/ Montserrat Roig, 2

Lleida- Catalonia-Spain

Telf: +34973702403 / Fax: +34973702426

e-mail: secretaria@cmb.udl.es

Lleida, 19 de Mayo de 2014

Dr. Ferrán Barbé Illa, profesor titular de la Universidad de Lleida,
Dr. Valentín Huerva Escanilla, doctor en Medicina por la Universidad de Zaragoza, como directores;
Dra. Carmen Jurjo Campo, doctora en Medicina por la Universidad de Barcelona, como tutora;
del trabajo de Tesis Doctoral "Patología Ocular y el Síndrome de Apnea-Hipoapnea del Sueño", realizado por MªJesús Muniesa Royo, licenciada en Medicina y Cirugía por la Facultad de Medicina de Lleida,

CERTIFICAMOS

Que en el trabajo presentado para optar al Grado de Doctor de la Universidad de Lleida, se han alcanzado los objetivos fijados al inicio de la Tesis. El trabajo de la presente tesis se ha realizado en el Departamento de Cirugía de la Universidad de Lleida. La memoria que se presenta constituye un trabajo compacto que profundiza en la patología ocular asociada al síndrome de apnea-hipoapnea del sueño.
Por tanto, consideramos apto este trabajo para proceder a su lectura y defensa ante la comisión correspondiente.
Para que así conste firmamos la presente notificación en Lleida a 19 de Mayo de 2014.

Dr. Ferrán Barbé Illa Dr. Valentín Huerva Escanilla Dra. Carmen Jurjo Campo

Als meus pares,

A les meves filles estimades.

Lo que sabemos es una gota de agua; lo que ignoramos es el océano.

Isaac Newton (1642-1727). Matemático y físico británico.

ÍNDICE

ÍNDICE DE TABLAS

A C R Ó N I M O S (por orden alfabético)

ASETCIRC	Asociación Española de Tecnología, Cirugía de Implantes, Refractiva y Córnea
AV	agudeza visual
CPAP	presión positiva continua en la vía aérea (siglas en inglés de Continuos positive airway pressure)
DS	desviación estándar
EEG	electroencefalograma
FRC	factor de resistencia corneal
GCC	grosor corneal central
GNT	glaucoma normotensional
GPAA	glaucoma primario de ángulo abierto
HC	histéresis corneal
IAH	índice de apnea-hipoapnea
IMC	índice de masa corporal
IRB	Institut de Recerca Biomèdica
JCR	Journal Citation Report
MIR	Médico Interno Residente
ORA	Analizador de Respuesta Ocular (siglas en inglés de Ocular Analyzer Response)
PIO	presión intraocular
PSG	polisomnografía
SAHS	síndrome de apnea-hipoapnea del sueño
SECOIR	Sociedad Española de Cirugía Ocular Implanto Refractiva
SEPAR	Sociedad Española de Neumología y Cirugía Torácica
SOCAP	Sociedad Catalana de Neumología
SPL	síndrome del párpado laxo

Parte I

T E S I S

PRESENTACIÓN

La presente tesis doctoral se estructura según las directrices de la normativa para la presentación de tesis doctorales en formato de artículos, aprobada por el Acuerdo num. 19/2002 de la Junta de Gobierno del 26 de febrero del 2002 de la Universidad de Lleida.

Los estudios presentados en la presente tesis doctoral pertenecen a una misma línea de investigación iniciada en 2009 con el objetivo de profundizar y avanzar en la relación entre el síndrome de apnea-hipoapnea del sueño y la patología ocular. Los resultados obtenidos han aportado información relevante en este campo y han dado lugar a dos artículos publicados en revistas internacionales y a otros dos trabajos cuyos resultados pretenden ser publicados próximamente.

1. Muniesa MJ, Huerva V, Sánchez-de-la-Torre M, Martínez M, Jurjo C, Barbé F. The relationship between floppy eyelid syndrome and obstructive sleep apnoea. *Br J Ophthalmol* 2013;97(11):1387-90.
   Impact Factor: 2.725 (JCR Q1)

2. Muniesa MJ, Sánchez-de-la-Torre M, Huerva V, Lumbierres M, Barbé F. Floppy eyelid syndrome as an indicator of the presence of glaucoma in patients with obstructive sleep apnea. *J Glaucoma* 2014;23(1):e81-5.
   Impact Factor: 1.825 (JCR Q2)

3. Muniesa MJ, March A, Sánchez de la Torre M, Huerva V[1,2], Jurjo C, Barbé F. Corneal Biomechanical Properties in Floppy Eyelid Syndrome. (Submitted)

4. Muniesa MJ,[1,2] Matias-Guiu X Sánchez-de-la-Torre M, González S, Vázquez B, Huerva V, Martínez M, Barbé F, MD. Evaluation of ocular surface changes in floppy eyelid syndrome by conjunctival impression cytology. (Submitted)

En los cuatro estudios, la doctoranda ha sido responsable de todos los aspectos referentes a la metodología de investigación, análisis de los resultados, interpretación de los mismos y extracción de conclusiones, así como de la redacción de los manuscritos.

RESUMEN

2.1 RESUMEN

Distintas patologías oculares se han relacionado con el síndrome apnea-hipoapnea del sueño (SAHS), incluyendo el síndrome del párpado laxo (SPL), glaucoma, queratocono, neuropatía óptica isquémica y papiledema. El SPL y el glaucoma son las patologías oculares más frecuentemente asociadas al SAHS, pero su incidencia y su patogenia relacionada con el SAHS todavía están en discusión.

Con el objetivo de profundizar en la relación entre la patología ocular y el SAHS se han realizado cuatro estudios.

En el primer estudio (Muniesa et al. *Br J Ophthalmol* 2013) se determinó la prevalencia de hiperlaxitud palpebral y de SPL en pacientes con SAHS, así como la prevalencia de SAHS en pacientes con SPL. La prevalencia de SPL entre pacientes con SAHS fue del 16% y la prevalencia de SAHS entre pacientes con SPL fue del 85%, de los cuales, el 65% tenían SAHS severo. Los pacientes con SAHS, presentaban de forma significativa, una mayor hiperlaxitud palpebral respecto a los pacientes sin SAHS.

En el segundo estudio (Muniesa et al. *J Glaucoma* 2014) se investigó si el SPL podría ser un indicador de glaucoma entre la población con SAHS. La prevalencia de glaucoma entre los pacientes con SAHS pero sin SPL fue del 5.3%, mientras que entre los pacientes con SAHS y con SPL, alcanzó el 23%, siendo significativamente más alta. Estos datos sugieren que el SPL podría ser un indicador útil para detectar los pacientes con SAHS que tengan más probabilidades de tener glaucoma.

En el tercer estudio (Muniesa et al.) se evaluó la biomecánica corneal en pacientes con SPL y pacientes sin SPL mediante el Analizador de Respuesta Ocular (ORA). Los resultados mostraron que los pacientes con SPL presentaban una histéresis corneal significativamente más baja, sugiriendo que en el SPL existen cambios estructurales adicionales.

En el cuarto estudio (Muniesa et al.) se evaluaron los cambios que el SPL produce en la superficie ocular mediante citología de impresión conjuntival comparando pacientes con SPL y pacientes sin SPL. Los pacientes con SPL presentaron unos cambios significativos en el epitelio conjuntival caracterizados por un aumento de la metaplasia escamosa y una disminución de las células caliciformes.

2.2 SUMMARY

Ophthalmic findings in patients with OSA included floppy eyelid syndrome (FES), glaucoma, keratoconus, ischemic optic neuropathy and papiledema.

FES and glaucoma are the most common ocular disorder associated with OSA but their prevalence and their pathogenesis associated with OSA is until unclear.

With the purpose to advance in the association between ocular pathology and OSA, it has been done four studies.

The first study (Muniesa et al. Br J Ophthalmol. 2013) determined the prevalence of eyelid hiperlaxity and FES in patients with OSA, and the prevalence of OSA in patients with FES. The results showed a prevalence of FES in OSA patients of 16% and a prevalence of OSA in FES patients of 85%, in those 65% had severe OSA. Patients with OSA had a significantly higher incidence of eyelid hyperlaxity than patients without OSA.

The second study (Muniesa et al. J Glaucoma 2014) wanted to investigate whether FES could be an indicator of glaucoma in patients with OSA. The prevalence of glaucoma in OSA patients without FES was 5.3%, and the prevalence of glaucoma in patients with OSA and with FES raised 23%. This prevalence was significantly higher in these patients. These results suggest that FES may offer a useful way to identify individuals with a greater probability of having glaucoma in the OSA population.

The third study (Muniesa et al.) determined the corneal biomechanical properties in patients with FES and compared them with patients without FES by Ocular Response Analyzer (ORA). The results showed that patients with FES had statistically lower corneal hysteresis values suggesting that corneal biomechanical properties could be changed in FES patients, reflecting additional structural changes in FES.

The final study (Muniesa et al.) evaluated the ocular surface changes in FES by conjunctival impression cytology features between patients with FES and patients without FES. Patients with FES were more likely to exhibit abnormal conjunctival cytology characterized by an increase in squamous metaplasia and a decrease in the number of goblet cells.

2.3 RESUM

Diferents patologies oculars s'han relacionat amb la síndrome d'apnea-hipoapnea del son (SAHS), incloent la síndrome de la parpella laxa (SPL), glaucoma, queratocon, neuropatia òptica isquèmica i papiledema. La SPL i el glaucoma són les patologies oculars més freqüentment associades a SAHS, però la seva incidència i patogènia relacionada amb SAHS encara està en discussió.

Amb l'objectiu de profunditzar en la relació entre la patologia ocular i SAHS, s'han realitzat quatre estudis.

En el primer estudi (Muniesa MJ, et al. Br J Ophthalmol. 2013) es va determinar la prevalença d'hiperlaxitud palpebral i de SPL en pacients amb SAHS, així com la prevalença de SAHS entre una població de pacients amb SPL. Els resultats mostraren una prevalença de SPL entre la població SAHS del 16% i una prevalença de SAHS entre els pacients amb SPL del 85%, dels quals el 65% tenien SAHS sever. Els pacients amb SAHS presentaven de forma significativa una major hiperlaxitud palpebral respecte als pacients sense SAHS.

En el segon estudi (Muniesa et al. J Glaucoma 2014) es va investigar si la SPL podia ser un indicador de glaucoma entre la població amb SAHS. La prevalença de glaucoma entre els pacients amb SAHS i amb SPL va ser del 5.3%, mentre que entre els pacients amb SAHS i amb SPL arribava al 23%, sent significativament més alta. Aquestes dades suggereixen que el SPL podria ser un indicador útil per detectar els pacients amb SAHS que tinguin més probabilitats de tenir glaucoma.

En el tercer estudi (Muniesa et al.) es va estudiar la biomecànica corneal en pacients amb SPL i sense SPL mitjançant l'Analitzador de Resposta Ocular (ORA). Els resultats mostraren que els pacients amb SPL presentaven una histèresi corneal significativament més baixa, suggerint que en la SPL existeixen canvis estructurals adicionals.

En el quart estudi (Muniesa et al.) es van avaluar els canvis que el SPL produeix en la superfície ocular mitjançant la citologia d'impressió conjuntival comparant pacients amb SPL amb pacients sense SPL. Els pacients amb SPL presentaren uns canvis significatius en l'epiteli conjuntival caracteritzats per un augment de la metaplasia escamosa i una disminució en el nombre de cèl.lules caliciformes.

INTRODUCCIÓN

3.1 EL SÍNDROME DE APNEA–HIPOPNEA DEL SUEÑO

El síndrome de apnea-hipopnea del sueño (SAHS) es uno de los trastornos del sueño más frecuentes que se caracteriza por episodios repetidos de reducción del flujo aéreo debido a una obstrucción parcial (hipoapneas) o completa (apneas), de la vía aéra superior que se colapsa mecánicamente. El SAHS afecta al 4-6% de los varones y al 2-4% de la mujeres de la población general adulta en edades medias (1), aumentando su prevalencia con la edad y siendo 2 o 3 veces más frecuente en varones que en mujeres (2). El SAHS está estrechamente relacionado con la obesidad (3). Clínicamente se caracteriza por somnolencia diurna y ronquido nocturno y suele ir asociado a apneas observables, arousals (despertar electroencefalográfico), fragmentación del sueño así como a hipoxia intermitente e hipercapnia. Se ha asociado a transtornos cardiovasculares, neurovasculares y neurocognitivos, inflamatorios y metabólicos secundarios. El índice de apnea-hipopnea (IAH) representa el número de apneas o hipoapneas por hora de sueño y es la forma habitual de definir la enfermedad. La presencia de un número anormal de apneas/hipoapneas durante el sueño asociado con síntomas relacionados con la enfermedad establece el diagnóstico de SAHS y permite cuantificar su gravedad. Es habitual en la práctica clínica el diagnóstico de SAHS si el IAH es $\geq$ 10/h y se acompaña de sintomatología. La prueba de referencia para establecer el diagnóstico de SAHS es la polisomnografía (PSG) nocturna. Se trata del registro de variables respiratorias, cardíacas y neurofisiológicas, que permiten conocer la cantidad y la calidad del sueño, así como la repercusión de las apneas e hipoapneas en las distintas variables y la determinación del IAH (4-8). El tratamiento del SAHS incluye cambios en el estilo de vida como pérdida de peso y la aplicación de presión positiva continua en la vía aérea superior (continuos positive airway pressure –CPAP-). La CPAP estabiliza la vía aérea superior y evita su colapso, normalizando el IAH y la estructura del sueño.

3.2 PATOLOGÍA OCULAR Y SAHS

Existe evidencia científica que indica que los pacientes con SAHS tienen mayor incidencia de patología ocular incluyendo el SPL (9,10), glaucoma (11-16), queratocono (17), neuropatía óptica isquémica no arterítica (18-19), papiledema (20), corioretinopatía serosa central (21) y oclusiones venosas retinianas (22).

Diferentes mecanismos enlazan el SAHS con las distintas enfermedades oculares, como son: el estrés oxidativo (23,24), la activación simpática (25,26), la inflamación (27,28), la hipercoagulabilidad (29-32), la disfunción endotelial (33) y las alteraciones metabólicas (34).

La desregulación vascular asociada al SAHS puede desempeñar un papel clave en la neuropatía óptica isquémica no arterítica y en las oclusiones venosas retinianas que se han relacionado con el SAHS. La hipoxemia e hipercapnia secundaria a las apneas nocturnas provoca una vasodilatación cerebral que puede contribuir al papiledema así como al aumento de la presión intracraneal que puede asociarse a los pacientes obesos con SAHS (35). El aumento de los niveles de catecolaminas observado en pacientes con SAHS se ha relacionado con el riesgo aumentado de corioretinopatía serosa central en estos pacientes (36).

La presente tesis se centra en las enfermedades oculares más prevalentes asociadas al SAHS, como son el SPL y el glaucoma.

3.2.1 SÍNDROME DEL PÁRPADO LAXO

En 1981, Culbertson y Ostler describieron un enigmático trastorno palpebral, reportando 11 pacientes obesos con síntomas severos de disconfort ocular. Estos pacientes presentaban unos párpados superiores hiperlaxos que se evertían con una mínima tracción manual. El tarso presentaba una pérdida intrínseca de la rigidez permitiendo la deformación con facilidad. Una marcada conjuntivitis papilar estaba también presente. Esta condición fue denominada “el síndrome del párpado laxo” (9).

La descripción inicial de los pacientes con SPL respondía al fenotipo de varón obeso de edad media. Más recientemente, el mejor conocimiento del espectro demográfico del SPL ha incluido a las mujeres y a los niños como susceptibles a

padecer SPL (37,38), aunque el grupo de población más frecuentemente afectado por el SPL son varones obesos entre 40 y 69 años (39).

El SPL produce una significativa morbilidad ocular y es motivo frecuente de consulta por molestias oculares de larga evolución. Los síntomas generalmente son poco específicos, y eso justifica que se trate de una patología infradiagnosticada o de diagnóstico tardío. Los pacientes con SPL presentan síntomas oculares unilaterales o bilaterales que pueden ir desde la hiperemia ocasional e irritación hasta la sensación de cuerpo extraño, secreción mucoide, ojo seco, fotosensibilidad, visión borrosa, edema palpebral y úlceras corneales (40).

Es frecuente que el lado más afectado corresponda con el lado que preferentemente el paciente use para dormir. Algunos de los pacientes notan que durante el sueño se produce una eversión palpebral provocando el roce con la almohada, aumentando el disconfort y pudiéndose asociar a lesiones corneales. De modo que el SPL potencialmente puede causar patología ocular grave.

El tratamiento incluye medidas no quirúrgicas como lubricantes, oclusión o escudos oculares. Pero muchos pacientes son refractarios al tratamiento médico y el acortamiento quirúrgico del párpado resulta imprescidible para evitar la eversión palpebral y mejorar la sintomatología (41).

En las últimas décadas se ha avanzado en el conocimiento de la naturaleza de esta condición pero la etiología y la patogenía no están todavía resueltas. Las asociaciones clínicas del SPL también están todavía en debate.

La conjuntivitis papilar es una condición crucial para el diagnóstico de SPL (9). Los cambios epiteliales y estromales de la conjuntivitis papilar crónica pueden ser iniciados por una variedad de estímulos como la exposición crónica que pueden presentar los pacientes con SPL.

Diferentes alteraciones palpebrales se han asociado al SPL como la blefaroptosis, ptosis de pestañas (41) y dermatocalasia (42).

Las alteraciones a nivel de la película lagrimal y la disfunción de las glándulas de Meibomio pueden exacerbar el disconfort y las alteraciones de las superficie ocular en estos pacientes. Se ha demostrado una deficiencia lipídica lagrimal y un ojo seco evaporativo (43).

La exposición corneal que puede asociarse a la eversión palpebral, así como la inflamación crónica de la conjuntiva, contribuyen a la posible aparición de

queratopatía en los pacientes con SPL. La queratopatía punctata superficial es la alteración corneal más frecuentemente asociada al SPL. Otras alteraciones corneales incluyen las úlceras corneales recidivantes (44), queratitis filamentosa y adelgazamiento corneal (45).

Una de las asociaciones más interesantes y desconocidas es la asociación entre el SPL y el queratocono. El queratocono es una enfermedad progresiva de la cornea que adopta una forma cónica irregular debido a la alteración de la estrutura interna del tejido corneal. Donnefeld fue el primero que hizo una asociación explícita entre el SPL y el queratocono destacando que ambas patologías aparecían principalmente en el lado sobre el que dormía apoyado el paciente (46). El estrés mecánico se ha postulado como mecanismo patogénico entre el SPL y el queratocono (44,46,47).

3.2.2 SÍNDROME DEL PÁRPADO LAXO Y SÍNDROME DE APNEA–HIPOAPNEA DEL SUEÑO

La principal asociación sistémica del SPL es el SAHS. Gonnering and Sonneland (48) en 1987 reportaron un paciente con SPL y SAHS. En 1989, Goldberg et al (49) reportaron un paciente con SPL que tenía el síndrome respiratorio de Pickwickian, un término que se refiere a alteración respiratoria durante el sueño con hipercapnia, policitemia e insuficiencia cardiaca. Pero fue Woong en 1990 el primero en describir explícitamente esta importante asociación en tres de sus pacientes (50). Otros estudios posteriores han apoyado la asociación entre el SPL y el SAHS (10,51). La prevalencia de SPL entre la población con SAHS varía entre el 2% (10,52) y el 32% (51), según los diferentes estudios. Un número menor de estudios han abordado la cuestión sobre la prevalencia del SAHS entre la población con SPL (53,54). Dado que el SPL y el SAHS estan asociados de forma independiente con la obesidad, el sexo masculino y al aumento de edad, no está claro si el SPL y el SAHS estan casualmente asociados, si comparten factores de riesgo o si tienen una causa fisiopatogénica común.

El SAHS ha sido propuesto como una posible etiología del SPL y esta hipótesis ha sido apoyada en un estudio que trataba con éxito el SPL con el uso de la CPAP (55).

Los cambios en el SPL afectan a la matriz extracelular y a las fibras de colágeno con una pérdida de fibras elásticas del tarso y sobreexpresión de metalloproteinasas (56-59). Estos cambios se atribuyen a un estrés mecánico representando un mecanismo de protección local en respuesta al trauma mecánico repetido (60). La disminución en las fibras elásticas del tarso de los pacientes con SPL tiene particular interés en aquellos que proponen un relación fisiopatogénica entre el SPL y el SAHS. En la úvula de los pacientes con SAHS sometidos a úvulofaringoplastia se ha demostrado una pérdida de fibras elásticas y se ha correlacionado la severidad del SAHS con la desorganización de las fibras elásticas a nivel de la úvula distal (61). De modo que cambios similares a los descritos en el tarso de los pacientes con SPL, pueden ocurrir en los tejidos de la vía aérea superior de los pacientes con SAHS secundario al trauma mecánico repetido debido al colapso de dicha vía aérea en decúbito prono durante el sueño.

En el SAHS, posiblemente debido a la posición durante el sueño, hay una presión mecánica repetida sobre los párpados favoreciendo la eversión y el trauma. Parece que la severidad del SPL se correlaciona con la severidad del SAHS (15). La teoría de la isquemia-reperfusión también se ha implicado en la relación entre el SAHS y el SPL (62). El SAHS se caracteriza por una hipoxia durante el sueño. Además estos pacientes someten a los párpados a una presión determinada que induce isquemia a nivel del tarso. Según esta teoría, cuando el paciente se levanta, la reperfusión repentina del tarso genera una gran cantidad de radicales libres que dañan el estroma tarsal y causa la subsecuente migración de polimorfonucleares neutrófilos que contribuye a la conjuntivitis papilar y a cambios ectásicos en la cornea. Esta teoría ofrece una explicación alternativa a la correlación entre el lado en que duerme el paciente y la lateralidad del SPL.

En cualquier caso, la relación fisiopatogénica entre el SPL y el SAHS no está totalmente resuelta. Mecanismos asociados al SAHS como el estrés oxidativo, la inflamación o la disfunción endotelial, podrían contribuir a la alteración subyacente de los tejidos palpebrales en los pacientes con SPL, haciéndoles más vulnerables al estrés mecánico y a los cambios por isquemia-reperfusión.

3.2.3 GLAUCOMA Y SÍNDROME DE APNEA–HIPOPAPNEA DEL SUEÑO

El glaucoma se define como una neuropatía óptica progresiva multifactorial, cuyo principal factor de riesgo es el aumento de la presión intraocular. La pérdida de células ganglionares de la retina responsable de la neuropatía óptica glaucomatosa conlleva defectos permanentes en el campo visual pudiendo llegar a la ceguera irreversible. La prevalencia de glaucoma en la población general caucásica se estima del 2% (63,64). La mayoría de estudios atribuyen al SAHS una prevalencia aumentada de glaucoma, tanto de glaucoma normotensional (GNT) (14) como de glaucoma primario de ángulo abierto (GPAA) (11,14). La prevalencia de glaucoma entre la población con SAHS varía entre el 2% y el 9%, según los distintos trabajos (11-14,16). El origen de la asociación entre el glaucoma y el SAHS no es totalmente conocida. Algunas posibles causas del glaucoma normotensional (coagulación sanguinea alterada, enfermedad cerebrovascular, enfermedad vasoespástica y desregulación vascular del nervio óptico) son también consecuencia del SAHS. En los pacientes con SAHS, los prolongados y repetidos periodos de apnea durante la noche son acompañados de hipoxia intermitente y de un aumento de la resistencia vascular. Se ha sugerido que estos episodios de desregulación vascular, pueden comprometer la perfusión y la oxigenación del nervio óptico causando una neuropatía óptica glaucomatosa. La disminución descrita del grosor de la capa de fibras nerviosas de la retina en los pacientes con SAHS (65) así como su correlación con el IAH, apoya la relación entre la hipoxia y la pérdida de la capa de fibras nerviosas de la retina en estos pacientes. Del mismo modo, el aumento de la activación simpática y el estrés oxidativo, dos condiciones que se encuentran comúnmente en el SAHS, pueden contribuir al desarrollo de disfunción endotelial que acentuaría la desregulación vascular a nivel de la cabeza del nervio óptico. Pero parece que no sólo intervienen factores vasculares en la patogenia del glaucoma en el SAHS, si no que incrementos de la presión intraocular (PIO) han sido descritos. Se ha relacionado el IAH con el aumento de la presión intraocular (66) y los pacientes con SAHS han demostrado mayores fluctuaciones de la PIO durante las 24h del día, con valores más altos durante las horas

nocturnas. Además, el tratamiento con CPAP podría causar unos aumentos adicionales de la PIO, especialmente durante la noche (67), y la obesidad, tan estrechamente asociada al SAHS, puede inducir aumentos de la PIO durante los cambios posicionales del cuello por compresión del mismo (68).

A pesar de que SPL es una alteración ocular frecuentemente asociada al SAHS y que a su vez, el SAHS se ha relacionado con el glaucoma, la posible relación entre el SPL y el glaucoma ha sido poco estudiada.

HIPÓTESIS Y OBJETIVOS

4.1 HIPÓTESIS DE LA TESIS

La hiperlaxitud palpebral, el síndrome del párpado laxo y el glaucoma se relacionan estrechamente con el síndrome de apnea-hypopnea del sueño compartiendo una base fisiopatogénica común. La determinación de su prevalencia permitiría avanzar en la relación entre estas patologías y establecer unos criterios sobre las pautas de screening en la práctica clínica.

Para intentar explicar estas asociaciones, en esta tesis doctoral se han planteado las siguientes hipótesis de trabajo:

1. El SAHS podría ser una condición favorable para la existencia de una subyacente laxitud palpebral aumentada, estando el SPL estrechamente relacionado con la presencia de SAHS.

2. El SAHS se asocia a una mayor prevalencia de glaucoma y el SPL puede ser un factor de riesgo de glaucoma entre la población con SAHS.

3. En el SPL pueden existir cambios estructurales adicionales que afecten a otras estructuras oculares como la córnea, que podrían contribuir a explicar la asociación patogénica entre el SPL y otras patologías como el glaucoma o el queratocono.

4. Los pacientes con SPL presentarían unos cambios en la superficie ocular que contribuirían a explicar la frecuente sintomatología ocular que acompaña a esta patología.

4.2 OBJETIVOS DE LAS TESIS

Para intentar dar respuesta a las distintas hipótesis de trabajo, en esta tesis doctoral se han planteado los siguientes objetivos específicos:

1. Estudiar la prevalencia de hiperlaxitud palpebral y de SPL en pacientes con SAHS, así como determinar la prevalencia de SAHS en pacientes con SPL.

2. Estudiar la prevalencia de glaucoma en pacientes con SAHS así como determinar si la presencia del SPL puede ser un factor de riesgo de glaucoma entre la población con SAHS.

3. Estudiar los cambios en la biomecáncia corneal en los pacientes con SPL mediante el Analizador de Respuesta Ocular (ORA).

4. Estudiar los cambios en la superficie ocular de los pacientes con SPL mediante citología de impresión conjuntival.

ESTUDIO 1

Muniesa et al. *Br J Ophthalmol* 2013;97:1387-1390.

5.1 HIPÓTESIS

El SAHS podría ser una condición favorable para la existencia de una subyacente laxitud palpebral aumentada, estando el SPL estrechamente relacionado con la presencia de SAHS.

5.2 OBJETIVOS

1. Estudiar la prevalencia de hiperlaxitud palpebral y de SPL en pacientes con SAHS.
2. Determinar la prevalencia de SAHS en pacientes con SPL.

5.3 METODOLOGÍA

El periodo de inclusión de los pacientes fue de Septiembre 2008 hasta Enero 2011. Para el primer objetivo, se incluyeron 114 pacientes que de forma consecutiva se habían admitido para descartar SAHS en el Hospital Arnau de Vilanova y Hospital Santa María de Lleida, que aceptaron someterse a continuación a una exploración oftalmológica antes de iniciar tratamiento para el SAHS. Para el segundo objetivo, 45 pacientes con diagnóstico previo de SPL, fueron sometidos a un estudio de sueño para descartar SAHS. El protocolo y el consentimiento informado fue aprovado por el Comité de Ética de nuestro hospital. Todos los pacientes incluidos en el estudio firmaron el consentimiento informado.

Se recogió una historia médica y oftalmológica completa de todos los pacientes.

Los pacientes que habían sido sometidos a cirugía palpebral o cualquier antecedente que pudiera afectar a la función de los párpados, no fueron incluidos en el estudio.

ESTUDIO OFTALMOLÓGICO

El examen oftalmológico incluía la agudeza visual, examen del polo anterior mediante lámpara de hendidura y oftalmoscopia para el fondo de ojo. El examen de los párpados iba dirigido a determinar la laxitud palpebral y a obtener un diagnóstico de SPL. La medición de la distracción horizontal de los párpados del globo ocular medida en milímetros, como describió Iyengar y Khan (69), fue utilizada como criterio para determinar la laxitud palpebral. Una distancia mayor de 5mm para los párpados superiores y mayor de 6mm para los inferiores, fue considerada como significativa e indicativa de hiperlaxitud palpebral (16). Según los resultados dividimos los pacientes en tres grupos: el grupo 1 incluía pacientes con laxitud normal; el grupo 2 pacientes con hiperlaxitud palpebral; y el grupo 3 pacientes con SPL. El SPL se definió como la presencia de párpados superiores fácilmente evertibles con mínima tracción manual asociado a conjuntivitis papilar crónica del mismo párpado superior, que es la definición clínica del SPL (9).

ESTUDIO DE SUEÑO

El diagnóstico de SAHS fue realizado mediante polisomnografía (PSG) convencional o mediante un estudio cardio-respiratorio del sueño. La PSG incluía el registro de variables neurológicas: Electroencefalograma (EEG) (C3/A2 y C4/A1), electro-oculograma y electromiograma de variables respiratorias medidas por una cánula nasal y de variables tóraco-abdominales. La saturación de oxígeno se midió a través de pulsioxímetro en el dedo. El estudio cardio-respiratorio del sueño incluía los registros procedentes de la cánula nasal, de las bandas tóraco-abdominales, la saturación de oxígeno y la posición corporal. La apnea fue definida como la ausencia de flujo aéreo al menos durante 10 segundos y la hipoapnea fue definida como una reducción clara (50%) del flujo aéreo durante al menos 10 segundos. El IAH fue calculado según el número de apneas o hipoapneas por hora. El SAHS fue excluido si el IAH $<10h^{-1}$. Se consideró SAHS leve cuando el IAH estaba entre 10 y $20h^{-1}$, moderado cuando estaba entre 20 y $30h^{-1}$, y severo cuando el IAH$>30h^{-1}$.

ANÁLISIS ESTADÍSTICO

Las variables continuas fueron reportadas con la media ± desviación estándar (DS), y los rangos intercuartiles usando el test de Wilcoxon. Las variables categóricas fueron expresadas en porcentajes y comparadas usando el test de X^2 o el test exacto de Fisher. Los intervalos de confianza para la proporción de pacientes con SPL en el SAHS y de SAHS en los pacientes con SPL se basaron en un test exacto binomial. La asociación entre hiperlaxitud palpebral y SAHS fue evaluada mediante una regresión logística. Una $p < 0.05$ fue considerada estadísticamente significativa. Los modelos se ajustaron a la edad y al índice de masa corporal (IMC).

5.4 PRINCIPALES RESULTADOS

Objetivo 1:

1. Ciento-catorce pacientes fueron admitidos consecutivamente para descartar SAHS. El número de pacientes diagnosticados de SAHS fue de 89 (78%) y 25 de los 114 pacientes fueron considerados no-SAHS o controles (22%). Los sujetos con SAHS eran significativamente de más edad y de mayor IMC que los controles.

2. Entre los pacientes con SAHS, 9/89 tenían SAHS leve (10%), 24/89 tenían SAHS moderado (26.9%) y 56/89 SAHS severo (62.9%).

3. De los 89 pacientes con SAHS, 14 tenían SPL (16%) y 11 de los 14 pacientes con SPL tenían SAHS severo, 2 pacientes tenían SAHS moderado y 1 paciente tenía SAHS leve.

4. El porcentaje de pacientes con SPL entre los pacientes con SAHS severo, alcanzaba el 20%.

5. Dos de los 25 pacientes controles sin SAHS tenían SPL (8%).

6. Las diferencias entre la prevalencia de SPL entre pacientes con SAHS (16%) y sin SAHS (8%) no llegó a ser estadísticamente significativa.

7. La hiperlaxitud palpebral fue observada en el 60.67% de los pacientes con SAHS (54/89) y en el 32% de los pacientes sin SAHS (8/25). Estas diferencias eran estadísticamente significativas tras ser ajustadas a la edad y al IMC (p = 0.04).

Tabla 5.1. Categorización de los pacientes según variables clínicas y prevalencia de hiperlaxitud palpebral y SPL entre los pacientes con y sin SAHS.

	Pacientes con SAHS	Pacientes sin SAHS	P
Pacientes, n	89	25	
Edad, años	55.1±9.41	48.6±11.15	0.003
Sexo, masculino	75%	72%	0.79
IMC (kg/m^2)	32.3±5.32	29.2±4.93	0.004
IAH	43.00±23.17	4.43±1.88	<0.001
SPL, n (%)	14 (16%)	2 (8%)	0.51
Hipelaxitud palpebral, %	54 (60.67%)	8 (32%)	(0.004) 0.0474*

*Ajustado a la edad y al IMC.

Objetivo 2:

1. De los 45 pacientes con SPL que fueron sometidos a un estudio de sueño, 38 fueron diagnosticados de SAHS (84.4%). El 8% de los pacientes tenían SAHS leve (3/38), el 26.3% SAHS moderado (10/38) y el 65.7% SAHS severo (25/38).

Tabla 5.2. Variables clínicas y prevalencia de SAHS entre pacientes con SPL.

	Pacientes con SPL
Pacientes, n	45
Edad, años	66.42±8.30
Sexo, masculino %	86.7
IMC (kg/m^2)	31.53±4.94
IAH	44.52±27.03
Pacientes con SAHS, n %	38 (84.4%)
Pacientes con SAHS severo, n %	25 (65.7%)

CME

Follow the link from the online version of this article to obtain certified continuing medical education credits

The relationship between floppy eyelid syndrome and obstructive sleep apnoea

MªJesús Muniesa,[1,2] Valentín Huerva,[1,2] Manuel Sánchez-de-la-Torre,[2,3] Montserrat Martínez,[2,3] Carmen Jurjo,[1,2] Ferran Barbé[2,3]

[1]Ophthalmology Department, Hospital Universitari Arnau de Vilanova, Lleida, Spain
[2]Institut de Recerca Biomèdica de Lleida, Lleida, Spain
[3]Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES), Madrid, Spain

Correspondence to
MªJesús Muniesa Royo, Department of Ophthalmology, Hospital Universitari Arnau de Vilanova, Avenue Alcalde Rovira Roure, Lleida 80 25198, Spain; mariajesus.muniesa@gmail.com

Received 30 December 2012
Revised 15 February 2013
Accepted 17 March 2013
Published Online First 12 April 2013

ABSTRACT

Purpose To determine the prevalence of eyelid hyperlaxity and floppy eyelid syndrome (FES) in obstructive sleep apnoea (OSA), and the presence of OSA in FES.

Participants One-hundred and fourteen patients who had been consecutively admitted for OSA evaluation and 45 patients with FES in which sleep studies were recorded.

Methods Subjects underwent eyelid laxity measurement, slit-lamp examination and polysomnography.

Results Eighty-nine patients were diagnosed of OSA. Fourteen patients with OSA had FES (16%) and 54/89 (60.67%) had eyelid hyperlaxity. Two of the 25 non-OSA patients had FES (8%) and 8 of 25 (32%) had eyelid hyperlaxity. There was a significantly higher incidence of eyelid hyperlaxity in OSA than in non-OSA patients (p=0.004). Thirty-eight of the 45 patients with FES were diagnosed of OSA (85%) and 65% had severe OSA.

Conclusions OSA might be an independent risk factor for eyelid hyperlaxity and severe OSA is common in patients with FES.

INTRODUCTION

Floppy eyelid syndrome (FES) is an often underdiagnosed disorder of unknown pathogenesis that is characterised by lax upper eyelids that are easily distorted and everted with minimal traction, a soft and foldable tarsus, and chronic papillary conjunctivitis of the upper palpebral conjunctiva.[1 2] Since the initial description by Culbertson and Ostler in 1981,[1] one of the most consistently reported associations with FES is that of obstructive sleep apnoea (OSA).[3 4] OSA is characterised by recurrent, complete or partial, upper airway obstructions during sleep and it is usually diagnosed by overnight polysomnography.[5] OSA is associated with a high incidence of cardiovascular and neurovascular diseases.[6] Woog was the first to specifically identify this important association between FES and OSA in three patients in 1990.[7] The prevalence of FES in the OSA population varies from 2%[8 9] to 32%[4] according to the reported series. A few investigations have raised the question of the frequency of OSA in patients with FES.[3 10] As FES and OSA are independently associated with obesity, male sex and increasing age, it is unclear whether OSA and FES are causally associated, whether they merely share common risk factors or whether they have a common pathophysiological cause.

The aim of this study was to establish the relationship between these two entities. The primary objective was to determine the prevalence of FES and eyelid hyperlaxity in a group of patients referred for suspected OSA. The second objective was to determine the presence of OSA in patients who had been previously diagnosed with FES in the oculoplastic unit.

MATERIAL AND METHODS

Subjects

The time period for patient inclusion was from September 2008 to January 2011. For the first objective, we included 114 patients consecutively admitted for OSA evaluation at the Arnau de Vilanova University Hospital and the Santa Maria Hospital, Lleida, Spain, who agreed to undergo an ophthalmologic examination. For the second objective, 45 patients with diagnosed FES made by an oculoplastic consultant (MJM), were subjected to overnight polysomnography to detect OSA. The protocol and informed consent were approved by the Ethics Committee of our hospital. All the subjects authorised the use and disclosure of protected health information. Patients who had undergone any type of surgical procedure to their eyelids or who had suffered from any type of ocular trauma or abnormality that could have affected their eyelid functions were excluded from the study.

Medical and ophthalmic examination

All subjects underwent a full medical and ophthalmic history. The slit-lamp examinations and lid laxity assessments were performed by the same ophthalmologist (MJM), who was blind to the results of sleep study. The ophthalmological examination included visual acuity, slit-lamp examination with anterior segment analysis and ophthalmoscopy. Eyelid examination was conducted specifically to evaluate eyelid laxity and obtain an FES diagnosis. Horizontal distraction from the globe was assessed as described by Iyengar and Khan[11] and measured in millimetres. We used this simple method of quantifying lid laxity using a ruler to measure the horizontal distraction of the lid from the globe. Lid distraction >5 mm for upper lids and >6 mm for lower lids was considered as significant and indicative of increased laxity.[12] The results were dichotomised for the purpose of analysis as increased laxity were present or absent. In the absence of standardised evaluation, we chose consensus criteria upon which to score the laxity in three groups: group 1 was normal laxity; group 2: asymptomatic eyelid hyperlaxity. Patients were defined as having eyelid hyperlaxity if either lid was graded positive for increase in laxity[8]; and group 3: FES defined as easily evertible lids and

Linked

http://dx.doi.org/10.1136/bjophthalmol-2013-303416

To cite: Muniesa MJ, Huerva V, Sánchez-de-la-Torre M, *et al*. *Br J Ophthalmol* 2013;**97**:1387–1390.

papillary conjunctivitis in the same upper eyelid, which is the clinical definition of FES.[1] Different grades of FES were included in this group. Easy lid eversion was characterised by elastic upper lids that became easily distorted and everted with minimal superolateral traction.[9 10]

Sleep studies

Diagnosis of OSA was reached on the basis of either conventional polysomnography or of a cardio-respiratory sleep study. All the sleep studies were analysed manually at each participating centre using standard criteria.[13] The sleep score was performed by technicians not involved in the study. The polysomnographies included continuous recording of neurological variables: EEG (C3/A2 and C4/A1), electro-oculogram and electromyogram. Breathing variables were scored according to the flow tracing provided by a nasal cannula and thermistor. Thoraco-abdominal motion was measured with thoracic and abdominal bands. Oxygen saturation was recorded with a finger-pulse oximeter. The cardio-respiratory sleep study included, at the minimum, continuous recording from the nasal cannula, thoraco-abdominal motion, oxygen saturation and body position. Apnoea was defined as an absence of airflow for at least 10 s and hypopnoea was defined as a clear (50%) airflow reduction for at least 10 s, with a drop in oxygen saturation of at least 4% or an arousal. OSAs were defined as the absence of airflow in the presence of chest or abdominal wall motion. The apnoea–hypopnoea index (AHI) was calculated according to the average number of episodes of apnoea plus hypopnoea per hour of sleep or recording time. OSA was excluded when the AHI was AHI<10^{-1}. OSA severity was scored as mild when the AHI was between 10 and 20 h^{-1}<20, moderate when it was between 20 and 30^{-1}, and severe when the AHI>30^{-1}.[13]

Statistical analysis

Continuous variables were reported as the mean±SD, and the IQR using the Wilcoxon rank sum test. Categorical variables were reported as percentages and were compared using the χ^2 or Fisher exact test. CIs for the proportion of patients with FES in the OSA group and OSA in the FES group were based on an exact binomial test. The association between eyelid hyperlaxity and OSA was evaluated by logistical regression. A p value of <0.05 was considered statistically significant. Age- and body mass index (BMI)-adjusted models were also estimated.

RESULTS

One hundred and fourteen patients were consecutively admitted for OSA evaluation by polysomnography or cardio-respiratory sleep study. A categorisation of these patients based on reported clinical findings is presented in table 1. Eighty-nine patients were diagnosed with OSA (78%) and 25 of 114 patients were considered non-OSA patients or controls (22%). As expected, subjects with OSA were significantly older and had a higher BMI than control patients but there was no significant difference in gender and other medical conditions. Among the patients with OSA, 9/89 had mild OSA (10.1%), 24/89 had moderate OSA (26.9%) and 56/89 had severe OSA (62.9%). Fourteen patients (16%) diagnosed with OSA had FES. Eleven of 14 patients with FES (78.57%) had severe OSA, 2 patients had moderate OSA and 1 patient had mild OSA. The percentage of FES in patients with severe OSA reached 20%. Two of the 25 non-OSA patients were diagnosed with FES (8%). The difference of prevalence of FES in OSA patients (16%) and in non-OSA patients (8%) was not statistically significant. None of the FES patients had experienced spontaneous lid eversion when sleeping. The findings of these patients with FES are presented in table 2.

Table 1 Categorisation of patients admitted for OSA evaluation, based on reported clinical findings

	OSA patients (AHI≥10)	Non-OSA patients group (AHI<10)	p Value
Patients, n	89	25	
Age, years Mean (SD)	55.1±9.41	48.6±11.15	0.003
Gender, male	75%	72%	0.79
BMI (kg/m^2) Mean (SD)	32.3±5.32	29.2±4.93	0.004
AHI (h^{-1}) Mean (SD)	43.00±23.17	4.43±1.88	<0.001
Epworth mean (SD)	9.5±4.93	7.8±4.58	0.13
HTA	47%	35%	0.45
Diabetes	15%	10%	0.73
Dyslipidaemia	29%	30%	1
Smokers	23%	15%	0.80
COPD	8%	10%	0.67
Cardiovascular diseases	20%	5%	0.18
FES, n (%)	14 (16%)	2 (8%)	0.51
Eyelid hyperlaxity, n (%)	54 (60.67%)	8 (32%)	0.0474*

*Adjusted for age and BMI.
AHI, apnoea–hypopnoea/h index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, type 2 diabetes mellitus; Epworth, Epworth Sleepiness Scale score; FES, floppy eyelid syndrome; HTA, hypertension; OSA, obstructive sleep apnoea.

Eyelid hyperlaxity was observed in 60.67% (54/89) of the patients with OSA, and in 32% (8/25) of the non-OSA patients (p=0.0125). This significance remained when adjusted for age and BMI (3.06, 95% CI 1.04 to 9.78, p=0.0474).

Forty-five patients with diagnosed FES were subjected to overnight polysomnography to detect OSA. A categorisation of these patients based on reported clinical findings can be seen in table 3. Thirty-eight of the 45 patients (84.4%) with FES were diagnosed with OSA. Mild OSA was diagnosed in 8% (3/38) of these patients with FES, moderate OSA in 26.3% (10/38) and severe OSA in 65.7% (25/38).

DISCUSSION

In this study, the incidence of eyelid hyperlaxity was significantly higher in OSA than in non-OSA patients and this significance remained after adjusting for age and BMI. These results suggested that OSA might be an independent risk factor for eyelid hyperlaxity. However, the prevalence of FES in OSA patients was not significant, although the prevalence of FES between patients with severe OSA reached 20%. To the best of our knowledge, this study is the largest cohort of FES patients (n=45) used to detect OSA diagnosed by polysomnography, the international criteria for OSA diagnosis.[14] Among patients with FES, the prevalence of OSA reached 85% and most of them had severe OSA. This prevalence contrasts with the prevalence of OSA in the general population estimated to be 2% to 5% in middle-aged populations,[15] and with the prevalence of OSA in obese population, estimated at 40%.[16] Therefore, this association between OSA and FES appears not to represent an epiphenomenon only. McNab[3] reported a cumulative series of 50 FES patients of whom 48 (96%) had a history of sleep disturbed breathing, and 26 of the 27 patients undergoing

Table 2 Data of patients admitted for OSA evaluation with floppy eyelid syndrome

Case No	Age (years)	Sex	BMI (kg/m^2)	AHI (h^{-1})	OSA grading	Side	Preferred sleeping pattern	Other diseases
1	61	M	41	49	Severe	R=L	Alternating	HTA, tabaqism
2	64	M	30	26	Moderate	R=L	Right	CVD, COPD, Dyslipidaemia
3	66	F	33	52	Severe	L>R	Left	CVD, COPD
4	69	M	31	76	Severe	R=L	Alternating	HTA, DM
5	61	M	43	26	Moderate	R=L	Alternating	Dyslipidaemia
6	54	M	43	37	Severe	L>R	Alternating	
7	54	M	29	36	Severe	R=L	Alternating	HTA
8	65	M	34	61	Severe	R=L	Alternating	HTA, CVD, Dyslipidaemia
9	60	M	32	76	Severe	L>R	Left	DM
10	57	F	47.7	36.7	Severe	R>L	Alternating	HTA, Tabaqism
11	61	F	33.7	83.57	Severe	R>L	Right	HTA
12	59	M	30.1	6.9	Normal	R=L	Left	HTA, CVD
13	62	M	37.41	43.52	Severe	L>R	Alternating	HTA
14	48	M	32	5.4	Normal	R=L	Right	Dyslipidaemia
15	72	M	33.8	47.5	Severe	R=L	Right	Smoker
16	45	F	49	11.4	Mild	R>L	Right	

AHI, apnoea–hypopnoea/h index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, type 2 diabetes mellitus; HTA, hypertension; OSA, obstructive sleep apnoea; SPK, superficial punctate keratopathy.

polysomnography were confirmed to have OSA. Ezra *et al*[10] studied OSA in 102 patients with FES using the Epworth daytime somnolence score, which is a method not considered valid for OSA diagnosis.

The reported prevalence of FES in OSA varies in different studies. The range of reported rates of FES prevalence (2.3–32%) includes studies by Robert *et al*,[8] 1/46, 2.2%; Karger *et al*,[9] 1/44, 2.3%; McNab,[3] 3/20, 15%; Kadyan *et al*,[12] 28/89, 31.5%.%; Mojon *et al*,[4] 14/44, 32%; and Chambe *et al*,[17] 23/89, 25.8%. A consensus has clearly not been reached. Kadyan *et al*[12] used only oximetry, which is a method not considered valid for OSA diagnosis,[14] McNab *et al*[3] had a very low patient sample size and Monjon *et al*[4] lacked any adjustment for age or BMI. Karger *et al*[9] used polysomnography for OSA diagnosis and showed an association between subjectively easy eversion and OSA when they studied 15 non-OSA patients and 44 OSA patients, but their findings lost statistical significance when they adjusted for age and BMI. Our results were comparable to the results of a recent study by Chambe *et al*[17] with 89 patients with OSA diagnosed with overnight respiratory polygraphy and 38 non-OSA patients, in which FES prevalence was 15.8% in non-OSA patients and 25.8% in OSA population (not significant), with a significant correlation between OSA severity and FES and eyelid laxity. So, the present study features one of the largest cohort of non-treated OSA patients diagnosed using a method considered valid for OSA diagnosis,[14] which has been used to detect FES.

Table 3 Categorisation of FES patients, based on reported clinical findings

	FES patients
Patients, n	45
Age, years Mean (SD)	66.42±8.30
Gender, male %	86.7
BMI (kg/m^2) Mean (SD)	31.53±4.94
AHI (h^{-1}) Mean (SD)	44.52±27.03
OSA patients, n %	38 (84.4%)
Severe OSA patients, n %	24 (64.7%)
HTA	26.7%
Diabetes	13.3%
Dyslipidaemia	15.6%
COPD	17.8%
Smokers	6.7%
Cardiovascular diseases	17.8%

*Adjusted for age and BMI.
AHI, apnoea–hypopnoea/h index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, type 2 diabetes mellitus; FES, floppy eyelid syndrome; HTA, hypertension; OSA, obstructive sleep apnoea.

Our results suggested that OSA could be a subset of lax eyelid conditions and it would appear that once the degree of laxity reaches a certain threshold, patients run the risk of developing FES with inflammatory sequelae of the conjunctiva, cornea and tear film.[18] OSA has been suggested as a possible cause for FES in a report that showed that FES could be resolved by simply making use of a continuous positive airway pressure mask.[19] There are different aetiological hypotheses about the association between FES and OSA. In their initial report, Culbertson and Ostler proposed that repeated mechanical trauma was the cause of papillary conjunctivitis, but they did not offer any hypothesis to explain the associated elasticity. Netland *et al*[20] were the first to point to abnormalities in elastic fibres, reporting a decrease in the amount of tarsal elastin. However, it still remains unclear whether this depletion of elastic fibres is causative or secondary. Schlotzer-Schrehardt *et al*[21] demonstrated a substantial loss of elastic fibres and ultrastructural abnormalities in residual fibres, together with an increased expression of elastin-degrading enzymes in the tarsus and skin of eyelid specimens from FES patients. These changes in elastic fibres are of particular interest to those who have proposed a link between FES and OSA. It has also been observed that uvula tissue from patients with OSA undergoing uvulopharyngoplasty exhibit a loss of elastic fibres.[8 20 22] These changes could explain how OSA, eyelid hyperlaxity and FES could be different manifestations of the same disease. The finding in our study of a significant association between eyelid hyperlaxity and OSA seems to support this

hypothesis. Furthermore, the proposed link between OSA and FES has had quite a strong influence on the ischaemia–reperfusion theory. McNab[23] claimed that an association may exist between sleeping posture and pressure on the eye, exacerbated by hypoxia, inducing ischaemia–reperfusion injury. Previous evidence confirmed that an association with sleep has been suggested because FES is commonly more symptomatic on the side the patient is used to sleeping on.[24] But this association is not perfect, as we can see in the present study, and this has led to doubts being cast over the mechanical theory.[25]

Clinicians should be aware of the association between FES and OSA so that underlying OSA can be detected in FES patients, and the sleep physician may be the first to detect the ocular symptoms of FES in patients with known OSA. This study confirmed that OSA is very common in FES but that FES is not so common among the general OSA population.

The limitations of this study include possible referral bias in the populations studied. The control group in our study raises the question of whether our data for non-OSA patients are representative of the general population. Several studies[12 17] had investigated FES prevalence in patients without OSA after these patients were recruited from a sleep unit. Kadyan *et al*[12] showed a FES prevalence of 3.8% (1/26) in non-OSA patients, and Chambe *et al*[17] of 15.8% (6/38). Our study presented a prevalence of 8% (2/25). These studies demonstrate that patients with OSA are significantly older and had increased BMI than patients without OSA; this suggested that our subject sample provided a good reflection of what would be observed in the general population. This could explain why the subjects were not age-matched and BMI-matched with controls.

In conclusion, eyelid hyperlaxity is associated with OSA, independent of age and BMI, suggesting that OSA might be an independent risk factor for eyelid hyperlaxity. Moreover, FES is strongly associated with OSA. The ophthalmologist may be the first physician to admit these patients for OSA evaluation and this allows the treatment of underlying OSA in patients with FES. This is an important point because OSA has a high association with morbidity and mortality and it is also linked to hypertension, heart failure, stroke and motor vehicle accidents, and in some cases, can even result in death.[13] It is important to consider routine screening of newly diagnosed FES patients for symptoms of sleep apnoea such as loud snoring or a history of apnoeic episodes and also to consider referral to a sleep specialist.

Contributors Arnau de Vilanova Universitary Hospital of Lleida. IRBLleida (Research biomedic Institute of Lleida).

Funding Instituto de Salud Carlos III (FIS PS09/02224). Societat Catalana de Pneumologia (SOCAP). Sociedad Española de Neumología y Cirugía torácica (SEPAR). These organisations had no role in the design or conduct of this research.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics Committee of Arnau de Vilanova Universitary Hospital of Lleida.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Culbertson WW, Ostler HB. The floppy eyelid syndrome. *Am J Ophthalmol* 1981;92:568–75.
2 Holbach LM. Diseases of the eyelid-conjunctival complex and corneal complications of lid disease. *Curr Opin Ophthalmol* 1995;6:39–43.
3 McNab AA. Floppy eyelid syndrome and obstructive sleep apnea. *Ophthal Plast Reconstr Surg* 1997;13:98–114.
4 Mojon DS, Godlblum D, Fleichhauer J, *et al*. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. *Ophthalmology* 1999;106:1182–5.
5 Flemons WW. Obstructive sleep apnea. *N England J Med* 2002;347:498–504.
6 Sanchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med* 2013;1:61–72.
7 Woog JJ. Obstructive sleep apnea and floppy eyelid syndrome. *Am J Ophthalmol* 1990;110:314–15.
8 Robert PY, Adenis JP, Tapie P, *et al*. Eyelid hyperlaxity and obstructive sleep apnea (O.S.A) syndrome. *Eur J Ophthalmol* 1997;7:211–15.
9 Karger RA, White WA, Park WC, *et al*. Prevalence of floppy eyelid syndrome in obstructive sleep apnea-hypopnea syndrome. *Ophthalmology* 2006;113:1669–74.
10 Ezra DG, Beaconsfield M, Sira M, *et al*. The associations of floppy eyelid syndrome: a case control study. *Ophthalmolgy* 2010;117:831–8.
11 Iyengar SS, Khan JA. Quantifying upper eyelid laxity in symptomatic floppy eyelid syndrome by measurement of anterior eyelid distraction. *Ophthal Plast Reconstr Surg* 2007;23:255.
12 Kadyan A, Asghar J, Dowson L, *et al*. Ocular findings in sleep apnoea patients using continuous positive airway pressure. *Eye (Lond)* 2010;24:843–50.
13 Rechtschaffen A, Kales A. *Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Publication No. 204. Washington, U.S. Government Printing Office, 1968.
14 Iber C, Ancoli-Israel S, Chesson A, *et al*. *The American Academy of Sleep Medicine manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. 1st edn. Westchester, IL: Academy of Sleep Medicine, 2007.
15 Bassiri AG, Guilleminault C. Clinical features and evaluation of obstructive sleep apnea-hypopnea syndrome. In: Kryger MH, Roth T, Dement WC. *Principals and practice of sleep medicine*. London: WB Saunders, 2000: 869–78.
16 Punjabi NM, Sorkin JD, KAtzel LI, *et al*. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *AM J Respir Crit Care Med* 2002;165:677–82.
17 Chambe J, Laib S, Hubbard J, *et al*. Floppy eyelid syndrome is associated with obstructive sleep apnoea: a prospective study on 127 patients. *J Sleep Res* 2012;21:308–15.
18 Fowler AM, Dutton JJ. Floppy eyelid Syndrome as a subset of lax eyelid condition: relationships and clinical relevance (an ASOPRS Thesis). *Ophthal Plast Reconstr Surg* 2010;26:195–204.
19 McNab AA. Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnea. *Clin Experiment Ophthalmol* 2000;28:125–6.
20 Netland PA, Sugrue SP, Albert DM, *et al*. Histopathologic features of the floppy eyelid syndrome. Involvement of tarsal elastin. *Ophthalmology* 1994;101:174–81.
21 Schlotzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, *et al*. The pathogenesis of floppy eyelid syndrome: involvement of matrix metalloproteinases in elastic fiber degradation. *Ophthalmology* 2005;112:694–6.
22 Abdal H, Pizzimenti JJ, Purvis CC. The eye in sleep apnea syndrome. *Sleep Med* 2006;7:107–15.
23 McNab AA. The eye and sleep. *Clin Experiment Ophthalmol* 2005;33:117–25.
24 Mc Naab A. The eye and sleep apnea. *Sleep Med Rev*, 2007;11:269–72.
25 Ezra D, Beaconsfield M, Collin R. Floppy eyelid syndrome: stretching the limits. *Surv Ophthalmol* 2010;55:35–46.

ESTUDIO 2

Muniesa et al. *J Glaucoma* 2014;23(1):e81-5

6.1 HIPÓTESIS

El SAHS se asocia a una mayor prevalencia de glaucoma y el SPL puede ser un factor de riesgo de glaucoma entre la población con SAHS.

6.2 OBJETIVOS

1. Determinar la presencia de glaucoma entre la población con SAHS, incluyendo el glaucoma primario de ángulo abierto y el glaucoma normotensional.
2. Investigar si el SPL puede ser un indicador de glaucoma en pacientes con SAHS.

6.3 METODOLOGÍA

El periodo de inclusión de los pacientes fue desde Septiembre 2008 a Diciembre 2011. Se incluyeron 152 pacientes que habían sido derivados a la Unidad del Sueño del Hospital Universitario Arnau de Vilanova y Hospital Santa María de Lleida para descartar SAHS, y que aceptaron someterse a un estudio oftalmológico para diagnosticar glaucoma. Se incluyeron 3 grupos de pacientes: 75 pacientes con SAHS pero sin SPL, 52 pacientes con SAHS y con SPL y 25 pacientes sin SAHS. Dos de los pacientes sin SAHS tenían SPL. Todos los pacientes se sometieron a un exámen oftalmológico completo para diagnosticar glaucoma según los criterios diagnósticos estándars.

El protocolo y el consentimiento firmado fue aprovado por el Comité de Ética de nuestro Hospital. Todos los pacientes firmaron el consentimiento informado.

Ninguno de los pacientes incluidos en el estudio tenía antecedentes de cirugía o trauma palpebral ni historia de cirugía intraocular en los 12 meses previos.

ESTUDIO DE SUEÑO

El diagnóstico de SAHS fue realizado mediante polisomnografía (PSG) convencional o mediante un estudio cardio-respiratorio del sueño. La PSG incluía el registro de variables neurológicas: EEG (C3/A2 y C4/A1), electro-oculograma y electromiograma, de variables respiratorias medidas por una cánula nasal y de variables tóraco-abdominales. La saturación de oxígeno se midió a través de pulsioxímetro en el dedo. El estudio cardio-respiratorio del sueño incluía los registros procedentes de la cánula nasal, de las bandas tóraco-abdominales, la saturación de oxígeno y la posición corporal. La apnea fue definida como la ausencia de flujo aéreo al menos durante 10 segundos y la hipoapnea fue definida como una reducción clara (50%) del flujo aéreo durante al menos 10 segundos. El IAH fue calculado según el número de apneas o hipoapneas por hora. El SAHS fue excluido si el IAH $<10h^{-1}$. Se consideró SAHS leve cuando el IAH estaba entre 10 y $20h^{-1}$, moderado cuando estaba entre 20 y $30h^{-1}$, y severo cuando el IAH$>30h^{-1}$.

ESTUDIO OFTALMOLÓGICO

El estudio de los párpados fue dirigido específicamente para evaluar la hiperlaxitud palpebral y hacer un diagnóstico del SPL. EL SPL se definió como la fácil eversión del párpado superior con la tracción manual asociado a conjuntivitis papilar crónica del mismo párpádo, que es la definición clínica del SPL (9).

La evaluación oftalmológica incluía: la agudeza visual (AV) mejor corregida, refracción, exámen del polo anterior en lámpara de hendidura, medida de la presión intraocular (PIO) con el tonómetro de aplanación de Goldman, paquimetría ultrasónica, gonioscopia y estudio del campo visual con campímetro Humprey (programa SITA-standard, test central 24-2). Tras dilatación pupilar se estudió la morfología del nervio óptico y el grosor de la capa de fibras nerviosas de la retina mediante tomografía de coherencia óptica (Stratus OCTm Carl Zeiss Ophthalmic Systems Inc.).

Los criterios utilizados en el presente estudio para definir glaucoma, independientemente de la PIO, fueron los siguientes: polo anterior y gonioscopia

normal, daño glaucomatoso del nervio óptico con asimetría en la excavación papilar y adelgazamiento del anillo neuroretiniano y/o hemorragias del disco óptico y/o defectos en la capa de fibras nerviosas de la retina, defectos glaucomatosos en el campo visual y progresión del daño del nervio óptico y de los defectos en el campo visual. Para el dignóstico de GPAA, la PIO sin tratamiento debía ser > 21mmHg y <22mmHg para el diagnóstico de GNT. Si los pacientes estaban diagnosticados de glaucoma previamente al presente estudio, se les consideraba que tenían diagnóstico previo de glaucoma (DPG).

ANÁLISIS ESTADÍSTICO

Todos los resultados se expresaron como media ± DS. El analísis estadístico de los datos demográficos, polisomnográficos y oftalmológicos fueron realizados mediante el test de la *t* de Student. La prevalencia de glaucoma fue calculada desde la proporción de pacientes con evidencia de glaucoma. Se usó el test de Mann-Whitney para analizar los resultados entre grupos. El 95% del intervalo de confianza fue usado para comparar la prevalencia de glaucoma entre nuestros pacientes con SAHS y la prevalencia de glaucoma en pacientes con SAHS publicada previamente. Cada correlación fue controlada por la edad y el IMC. La $p < 0.05$ fue considerada estadísticamente significativa.

6.4 PRINCIPALES RESULTADOS

Objetivo 1:

1. La prevalencia de glaucoma en los 127 pacientes con SAHS, incluyendo los 75 pacientes con SPL y los 52 pacientes sin SPL, fue del 12.9%.

Objetivo 2:

1. La prevalencia de glaucoma en los pacientes con SAHS pero sin SPL fue del 5.3% (4/75). Un paciente tenía GPAA y 3 pacientes tenían DPG.

2. La prevalencia de glaucoma en los pacientes con SAHS y con SPL fue del 23.07%. Séis pacientes tenían GNT, 5 tenían GPAA y un paciente tenía DPG.

3. Las diferencias en la prevalencia de glaucoma en pacientes con SAHS y con SPL y en pacientes con SAHS y sin SPL, fueron estadísticamente significativas tras ajustarse a la edad (p = 0.04).

4. El glaucoma se asoció a la presencia del SPL independientemente del IMC.

Tabla 6.1. Categorización de los pacientes según variables clínicas y prevalencia de glaucoma entre pacientes con SAHS, con y sin SPL, y pacientes sin SAHS.

	Pacientes con SAHS sin SPL	Pacientes con SAHS y SPL	P	Pacientes sin SAHS
N	75	52		25
Edad, años	54.3±9.25	63.66±9.01	0.000	48.6±11.15
Sexo, masculino %	76%	84.6%	0.145	72%
IMC (kg/m^2)	31.4±4.54	34.36±6.03	0.011	29.2±4.93
IAH	42.21±23.6	45.73±24.0	0.348	4.10±1.61
Glaucoma, n%	4/75 (5.33%)	12/52 (23.07%)	0.004 0.04*	0%

*Ajustado a la edad y al IMC.

ORIGINAL STUDY

Floppy Eyelid Syndrome as an Indicator of the Presence of Glaucoma in Patients With Obstructive Sleep Apnea

MaJesús Muniesa, MD,† Manuel Sánchez-de-la-Torre, PhD,†‡§‖*
Valentín Huerva, MD,† Marina Lumbierres, MD,†‡§‖ and Ferran Barbé, MD†‡§‖*

Purpose: The aim of the study was to investigate whether floppy eyelid syndrome (FES) could be an indicator of glaucoma in patients with obstructive sleep apnea (OSA).

Materials and Methods: A total of 152 patients were included: 75 patients with OSA and without FES; 52 patients with OSA and FES; and 25 non-OSA patients. The presence of FES was defined by easy upper eyelid eversion and tarsal papillary conjunctivitis. All the patients underwent a complete ophthalmologic examination to diagnose glaucoma; this included computerized perimetry and retinal fiber layer measurements with optical coherence tomography.

Results: The prevalence of glaucoma in OSA patients without FES was 5.33% (4/75). One patient had primary open-angle glaucoma and 3 had previously diagnosed glaucoma. The prevalence of glaucoma in OSA patients with FES was 23.07% (12/52). Six patients had normal-tension glaucoma, 5 had primary open-angle glaucoma and one patient had previously diagnosed glaucoma. None of the 25 patients without OSA had glaucoma. The difference in the prevalence of glaucoma between OSA patients without FES (5.3%) and OSA patients with FES (23.07%) was statistical significant ($P = 0.004$). When adjustments were made for age and body mass index, this significance remained ($P = 0.04$).

Conclusions: These data suggest that FES may offer a useful way to identify individuals with a greater probability of having glaucoma in the OSA population.

Key Words: glaucoma, floppy eyelid syndrome, obstructive sleep apnea

(*J Glaucoma* 2014;23:e81–e85)

Floppy eyelid syndrome (FES) is a frequently underdiagnosed disorder that is characterized by lax upper eyelids, which are easily distorted and everted with minimal traction; it is also associated with chronic papillary conjunctivitis of the upper palpebral conjunctiva.[1] Since its initial description by Culbertson and Ostler,[2] one of the most consistently reported associations of FES is with obstructive sleep apnea syndrome (OSA).[3,4] The prevalence of FES in the OSA population varies from 2%[1] to 32%,[4] according to the reported series. OSA is characterized by recurrent complete or partial upper airway obstructions during sleep. Each episode of apnea or hypopnea is associated with hypoxemia and hypercapnia and associated cardiorespiratory disturbances, with a high risk of cardiovascular and neurovascular complications.[5] The prevalence of OSA is estimated to be between 2% and 5% in middle-aged populations.[6] Ophthalmologic findings in patients with OSA include FES,[2,7] keratoconus,[8] papilledema,[9] optic neurophathy,[10] and glaucoma.[11–16] The prevalence of glaucoma in the OSA population varies from 2% to 9% according to the reported series.[11–16] Only 2 studies[3,7] have previously examined the association between FES and glaucoma. McNab[3] reported 1 in 8 patients (12.5%) with FES and OSA having normal-tension glaucoma (NTG). Robert et al[7] reported that 6 of 69 patients (8.7%) with sleep disorders screened for FES were treated for glaucoma. Unfortunately, they did not verify which of the glaucoma patients had OSA.

The aim of the present study was to determine whether the presence of FES is associated with a higher prevalence of glaucoma in OSA patients in order to determine whether FES could be an indicator of glaucoma in patients with OSA.

MATERIALS AND METHODS

The study design was cross-sectional. The period for patient inclusion was September 2008 to December 2011. We included 152 patients who had been admitted for OSA evaluation at the Arnau de Vilanova University Hospital and Santa Maria Hospital, Lleida, Spain and who agreed to undergo an ophthalmologic examination to diagnose glaucoma. Seventy-five patients had OSA without FES; 52 patients had OSA and FES; and 25 patients did not have OSA. Two of the non-OSA patients had FES. All the patients were subjected to a complete ophthalmologic examination to diagnose glaucoma. They were examined by a glaucoma expert (MaJ.M.R.), who was blinded to the results of the sleep study, according to standard diagnostic criteria.

None of the patients included had undergone any form of surgical intervention to the eyelid or had suffered from any type of ocular trauma or abnormality that could have affected eyelid function, nor did any of them have a history of ocular surgery in the previous 12 months. Patients with known neurological or psychiatric disorders were not included in the study. The protocol and informed consent were both approved by the Ethics Committee of our hospital, and informed consent was obtained in all cases.

Received for publication July 13, 2012; accepted April 22, 2013.
From the Departments of *Ophthalmology; ‡Pneumology, Hospital Universitari Arnau de Vilanova; †Institut de Recerca Biomèdica de Lleida (IRB Lleida); §Hosptital Santa Maria, Lleida; and ‖Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES), Madrid, Spain.
Disclosure: Supported by Instituto de Salud Carlos III (FIS PS09/02224), Societat Catalana de Pneumologia (SOCAP), Sociedad Española de Neumología y Cirugía torácica (SEPAR). These organizations had no role in either the design or execution of this research. The authors declare no conflict of interest.
Reprints: MaJesús Muniesa, MD, Department of Ophthalmology, Hospital Universitari Arnau de Vilanova, Avinguda Alcalde Rovira Roure 80, 25198 Lleida, Spain (e-mail: mariajesus.muniesa@gmail.com).

DOI: 10.1097/IJG.0b013e31829da19f

Sleep Studies

Diagnosis of OSA was made on the basis of either conventional polysomnography or a cardiorespiratory sleep study. All the sleep studies were individually analyzed at each participating center by applying standard criteria.[17] The polysomnographies included the continuous recording of neurological variables: electroencephalogram (C3/A2 and C4/A1), electrooculogram, and electromyogram. Breathing variables were scored according to a flow tracing provided by a nasal cannula and thermistor. Thoracoabdominal motion was measured with thoracic and abdominal bands. Oxygen saturation was recorded with a finger-pulse oximeter. The cardiorespiratory sleep study included (as a minimum): a continuous recording from the nasal cannula, thoracoabdominal motion, oxygen saturation, and body position. Apnea was defined as an absence of airflow for at least 10 seconds, and hypopnea was defined as a clear (50%) airflow reduction for at least 10 seconds, with a drop in oxygen saturation of at least 4% on arousal. OSA was defined as the absence of airflow in the presence of chest or abdominal wall motion. The apnea-hypopnoea index (AHI) was calculated according to the average number of episodes of apnea plus hypopnea per hour of sleep or recording time. Sleep stages were scored as: normal, AHI $< 10^{-1}$; mild OSA, $10^{-1} \geq$ AHI $< 20^{-1}$; moderate OSA, $20^{-1} \geq$ AHI $< 30^{-1}$; and severe OSA, AHI $\geq 30^{-1}$.[17]

Ophthalmic Examination

Eyelid examination was specifically conducted to evaluate eyelid laxity and to obtain an FES diagnosis. FES was defined as easily evertible lids and the presence of papillary conjunctivitis in the same upper eyelid, which is the clinical definition of FES.[1,2] Easy lid eversion was characterized by increased laxity in the upper lids that became easily distorted and everted with only minimal superolateral traction.

The eye examination included: best-corrected visual acuity with a recording of the refractive correction; slit-lamp biomicroscopy of the anterior segment; Goldmann applanation tonometry performed with the same tonometer; ultrasonic corneal pachymetry; gonioscopy; and visual field analysis with the Humphrey Field Analyzer (SITA-standard program, central 24-2 threshold test). Visual field tests were repeated 1 week later if significant fixation losses and/or false positives or negatives were detected to be >15%.[18] Patients with OSA also often tend to exhibit losses of attention during these tests. We also repeated the visual field test 4 months later in the case of patients suspected of suffering from glaucoma. After pupil dilatation, the morphology of the optic disc was assessed by stereoscopic slit-lamp biomicroscopy, using a fundus 3-mirror lens. The thickness of the retinal nerve fiber layer (RNFL) was assessed using optical coherence tomography (Stratus OCTm Carl Zeiss Ophthalmic Systems Inc.).

The following criteria were used to define glaucoma in our study, irrespective of the intraocular pressure (IOP): a normal-appearing anterior chamber angle on gonioscopy; glaucomatous optic disc damage with asymmetric cupping and thinning of the neuroretinal rim and/or optic disc hemorrhage and/or defects in RNFL thickness; glaucomatous visual field defects (Bjerrum and/or paracentral scotoma, nasal step, and altitudinal defects); and the progression of optic nerve damage and visual field defects. For the diagnosis of primary open-angle glaucoma (POAG), untreated IOPs had to remain at above 21 mm Hg and below 22 mm Hg for the diagnosis of NTG. If the patients had been diagnosed with glaucoma before the present study, we considered that they had previously diagnosed glaucoma (PDG).

Statistical Analysis

All the data were expressed as mean ± SD. Statistical analyses of the demographic data, polysomnographic recordings, and ophthalmologic examinations were performed using the unpaired Student *t* test. The prevalence of glaucoma was calculated from the proportion of patients with evidence of glaucoma. We used the Mann-Whitney test to analyze data between groups. Right and left eyes were analyzed separately. The 95% confidence interval was used to compare the prevalence of glaucoma in our OSA patients with the prevalence of glaucoma in OSA reported in previous publications. Spearman Rank correlation was also used whenever appropriate. Each correlation was controlled for age and body mass index (BMI). $P < 0.05$ was considered statistically significant. The language and environment for the R Foundation for Statistical Computing (Vienna, Austria) was also used.

RESULTS

The demographic data for the 152 patients included in the study are presented in Table 1 and divided according to the presence of OSA and FES.

The prevalence of glaucoma in the 127 patients with OSA, including 75 patients without FES and 52 patients with FES, was 12.9%. The prevalence of glaucoma in the OSA patients without FES was 5.3% (4/75) with a 95% confidence interval of 1.5%-13.1%. One patient had POAG

TABLE 1. Categorization of the Patients Included in the Study on the Basis of Reported Clinical Findings

	OSA Patients Without FES	OSA Patients With FES	*P*	Non-OSA Patients
N	75	52		25
Age	54.3 ± 9.25	63.66 ± 9.01	0.000	48.6 ± 11.15
Sex	76%	84.6%	0.145	72%
BMI	31.4 ± 4.54	34.36 ± 6.03	0.011	29.2 ± 4.93
AHI	42.21 ± 23.6	45.73 ± 24.04	0.348	4.10 ± 1.61
Glaucoma patients	4/75 (5.33%)	12/52 (23.07%)	0.004	0%
			0.04*	

*After adjusting for age and BMI.
AHI indicates apnea-hypopnea index; BMI, body mass index (kg/m^2); FES, floppy eyelid syndrome; OSA, obstructive sleep apnea.

TABLE 2. Comparison Between the Prevalence of Glaucoma in OSA Patients According to the Presence of FES Observed in the Present Study and Those Previously Reported

Prevalence of Glaucoma in the Present Study	Prevalence of Glaucoma in OSA Patients Published Previously	P
OSA patients without FES 5.3% (CI, 1.5%-13.1%)	3.4%[16]	0.299
	5.9%[13]	0.924
	5.6%[15]	0.990
	5.9%[14]	0.987
	7.2%[11]	0.610
OSA patients with FES 23.07% (CI, 11.2%-34.6%)	3.4%[16]	< 0.001
	5.9%[13]	< 0.001
	5.6%[15]	< 0.001
	5.9%[14]	< 0.001
	7.2%[11]	< 0.001

CI indicates confidence interval; FES, floppy eyelid syndrome; OSA, obstructive sleep apnea.

and 3 had PDG. The prevalence of glaucoma in patients with OSA and FES (12/52) was 23.07%, with a 95% confidence interval of 11.2%-34.9%. Six patients had NTG, 5 had POAG, and 1 patient had PDG. None of the 25 patients without OSA had glaucoma. A comparison between the prevalence of glaucoma in OSA patients according to the presence of FES observed in the present study and those previously reported is shown in Table 2. The difference in the prevalence of glaucoma between OSA patients without FES (5.3%) and OSA patients with FES (23.07%) was statistical significant ($P = 0.004$). When adjustments were made for age and BMI, this significance remained ($P = 0.04$). Glaucoma was associated with the presence of FES independently of BMI (Table 3). The demographic data and ophthalmologic findings for patients with OSA included in the study divided according to the presence or absence of glaucoma are presented in Table 4.

There was no association between AHI and the presence of glaucoma after adjusting for age and BMI; the adjusted coefficient was −0.079 and the *P*-value was 0.394. The Spearman correlation coefficient failed to show any correlation between the AHI and IOP, central corneal thickness, mean deviation of the visual field, and/or the average thickness of the RNFL (Table 5).

DISCUSSION

The high prevalence of glaucoma detected in our patients with FES and OSA (23.07%) suggested that FES could be a strong indicator of glaucoma in patients with OSA. The association between OSA and glaucoma has been suggested in several previous reports.[11–16] However, the prevalence of glaucoma in OSA patients with FES as a possible indicator of glaucoma had previously received relatively little formal study[3,7]: McNab[3] studied a smaller sample than the one included in the present study and did not include OSA patients without FES as a control group. Robert et al[7] did not state which of their glaucoma patients had OSA. Other published studies have shown the prevalence of glaucoma in OSA without taking into account the presence of FES in the OSA population. Geyer et al[12] reported that the prevalence of glaucoma in OSA patients was similar to that found in the general white population[19,20]: a 2% prevalence of glaucoma was found in patients with OSA diagnosed by polysomnography (5/228).

TABLE 3. Correlational Study Between the Presence of Glaucoma and Age and BMI

	Presence of Glaucoma
Age	
Correlation	0.393
P	0.000
BMI	
Correlation	0.039
P	0.693

BMI indicates body mass index (kg/m²).

TABLE 4. The Demographic Data and Ophthalmologic Findings for Patients With OSA Divided According to the Presence of Glaucoma

	OSA Patients Without Glaucoma	OSA Patients With Glaucoma	P
N	111	16	
Age (y)	56.2 ± 9.04	67.6 ± 8.30	0.001
BMI	32.31 ± 5.32	32.51 ± 4.21	0.691
AHI	44.17 ± 24.31	38.20 ± 18.00	0.507
VA RE	0.87 ± 0.15	0.80 ± 0.17	0.21
VA LE	0.85 ± 0.17	0.70 ± 0.3	0.09*
IOP RE	15.41 ± 3.15	19.35 ± 5.01	0.004*
IOP LE	14.92 ± 2.55	19.30 ± 5.34	0.000*
CCT RE	544.12 ± 34.06	548.83 ± 27.99	0.649
CCT LE	544.09 ± 35.20	547.09 ± 29.80	0.788
Average RNFL thickness RE	99.36 ± 11.12	79.29 ± 14.74	0.000*
Average RNFL thickness LE	96.07 ± 9.23	82.51 ± 13.38	0.001*
MD RE (dB)	−2.072 ± 2.20	−6.75 ± 4.34	0.000*
MD LE (dB)	−2.20 ± 2.03	−5.33 ± 3.48	0.003*
FES	40/111 (36%)	12/16 (75%)	0.123*

Data presented as mean ± SD.
*After adjusting for age.
AHI indicates apnea-hypopnea index; BMI, body mass index (kg/m²); CCT, central corneal thickness; FES, floppy eyelid syndrome; IOP, intraocular pressure; LE, left eye; MD, visual field mean deviation; RE, right eye; RNFL, retinal nerve fiber layer; VA, visual acuity.

TABLE 5. Spearman Correlations Between Apnea-Hypopnea Index and Ophthalmologic Findings

AHI Correlation	Adjusted Coefficient for AHI*	P*
IOP RE	−0.233	0.546
IOP LE	−0.144	0.712
CCT RE	−0.487	0.184
CCT LE	−0.436	0.241
MD (dB) RE	−0.082	0.834
MD (dB) LE	0.277	0.470
Average thickness RNFL RE	−0.151	0.698
Average thickness RNFL LE	0.028	0.943

*All the correlations were controlled for age and body mass index.
AHI indicates apnea-hypopnea index; CCT, central corneal thickness; IOP, intraocular pressure; LE, left eye; MD, mean deviation; RE, right eye; RNFL, retinal nerve fiber layer.

Kadyan et al[16] reported that the prevalence of open-angle glaucoma in OSA patients (3/89, 3.4%) was similar to that in a normal population (2%). In 2007, Sergi et al[13] reported 3 of 51 OSA patients (5.9%) with NTG; this suggested that the prevalence of NTG in OSA patients was higher than would normally be expected in a white population of the same age and that OSA may be an important risk factor for NTG. A recent study by Chambe et al[15] showed a prevalence of glaucoma in OSA patients diagnosed by overnight respiratory polygraphy of 5.6% (5/89). In 2010, Lin et al[14] reported a prevalence of 5.7% of NTG among patients with OSA (12/209) but no glaucoma patients among 38 non-OSA patients. Monjon et al[11] found a 7.2% prevalence of glaucoma among 69 patients with OSA who underwent a polysomnographic evaluation (5/69), which suggested a strong association between glaucoma and OSA. Our study confirmed the previously reported high correlation between glaucoma and OSA, with a 12.9% prevalence of glaucoma in all OSA patients. It is possible than this prevalence was higher than that reported in previous publications because of the large number of FES patients included in the present study. When we excluded the patients with FES, the prevalence of glaucoma in OSA patients was 5.3%, and this prevalence was not significantly different from that of glaucoma in patients with OSA that had been published previously. When we included only OSA patients with FES, the rate of prevalence reached 23%, and this was significantly higher than the prevalence of glaucoma in OSA patients reported in previous publications. These data supported the hypothesis that FES could be an important indicator of glaucoma in OSA patients. It is quite likely that age and BMI are also associated with the presence of glaucoma.[21,22] The observed differences in the prevalence of glaucoma between patients with OSA but without FES and those with both OSA and FES were statistically significant after adjusting for age and BMI. Glaucoma was associated with the presence of FES independently of BMI. Although age was a partial confounding factor in the relation between glaucoma and FES, its effect did not prevent these differences from being statistically significant. These results suggested that FES could be a risk factor for glaucoma in patients with OSA. Further, the presence of glaucoma in patients with OSA in the current study was not related to the severity of OSA defined by their AHI.

Therefore, FES could be useful for identifying individuals with more probability of having glaucoma amongst the OSA population. More studies are necessary to corroborate these results and to study whether FES could be an independent risk factor for glaucoma in patients without OSA.

Owing to the observational character of our study, the results obtained do not allow us to draw any conclusions about direct causal relationships between glaucoma, OSA, and FES.

Several reports have proposed a vascular etiology in glaucoma.[11,13] In patients with OSA, prolonged repetitive periods of apnea during sleep are accompanied by transient hypoxia and increased vascular resistance. It has been suggested that this episodic vascular impairment may compromise optic nerve head perfusion and oxygenation, causing glaucomatous optic neuropathy. The proposed link between OSA and FES has had quite a strong influence on the ischemia-reperfusion theory.[23] Hypoxic ischemia may contribute to optic nerve damage but would not necessarily be expected to do so by increasing IOP. We cannot, therefore, exclude the possibility of another factor also influencing glaucoma in OSA. In obese patients, increases in IOP during positional changes, in which the neck is compressed, have also been observed.[24] Both FES and OSA have been independently associated with obesity. Moreover, it has also been observed that uvula tissue from patients with OSA demonstrates a loss of elastic fibers.[25] Schlötzer-Schrehardt et al[26] reported a pattern of elastic fiber depletion in the tarsal connective tissue in FES. Culbertson and Ostler[2] hypothesized that a subtle form of underlying generalized connective tissue alteration could be responsible for eyelid laxity in FES. It could be possible that the elastic fiber depletion described in FES and OSA could indicate some of the characteristics present in other ocular structures, such as lamina cribosa or/and trabecular meshwork. These changes could increase the risk of glaucoma in OSA patients affected by FES. Further studies are necessary to corroborate this hypothesis.

In conclusion, FES may be a predictive factor for the presence of glaucoma in patients with OSA. Given the high prevalence of glaucoma in patients with OSA and FES observed in our study, we advise screening FES patients for glaucoma.

REFERENCES

1. Karger RA, White WA, Park WC, et al. Prevalence of floppy eyelid syndrome in obstructive sleep apnea-hypopnea syndrome. *Ophthalmology*. 2006;113:1669–1674.
2. Culbertson WW, Ostler HB. The floppy eyelid syndrome. *Am J Ophthalmol*. 1981;92:568–575.
3. McNab AA. Floppy eyelid syndrome and obstructive sleep apnea. *Ophthal Plast Reconstr Surg*. 1997;13:98–114.
4. Mojon DS, Godlblum D, Fleichhauer J, et al. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. *Ophthalmology*. 1999;106:1182–1185.
5. Masood A, Phillips B. Sleep apnoea. *Curr Opin Pulm Med*. 2000;6:479–484.
6. Bassiri AG, Guilleminault C. Clinical features and evaluation of obstructive sleep apnea-hypopnea syndrome. In: Kryger MH, Roth T, Dement WC, eds. *Principals and Practice of Sleep Medicine*. London: WB Saurnders; 2000:869–878.
7. Robert PY, Adenis JP, Tapie P, et al. Eyelid hyperlaxity and obstructive sleep apnea (O.S.A) syndrome. *Eur J Ophthalmol*. 1997;7:211–215.
8. Culbertson WW, Tseng SCG. Corneal disorders in floppy eyelid syndrome. *Cornea*. 1994;13:33–42.
9. Bucci FA Jr, Krohel GB. Optic nerve swelling secondary to the obstructive sleep apnea syndrome. *Am J Ophthalmol*. 1988; 105:428–430.
10. Mojon DS, Mathis J, Zulauf M, et al. Optic neuropathy associated with sleep apnea syndrome. *Ophthalmology*. 1998; 105:874–877.
11. Monjon DS, Hess C, Goldblum D, et al. High prevalence of glaucoma in patients with sleep apnea syndrome. *Ophthalmology*. 1999;106:1009–1012.
12. Geyer O, Cohen N, Segev E, et al. The prevalence of glaucoma in patients with sleep apnea syndrome: same as in the general population. *Am J Ophthalmol*. 2003;136:1093–1096.
13. Sergi M, Salermo DE, Rizzi M, et al. Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients. *J Glaucoma*. 2007;16:42–46.
14. Lin PW, Friedman M, Lin HC, et al. Normal tensión glaucoma in patients with sleep apnea/hypopnea syndrome. *J Glaucoma*. 2011;20:553–558.
15. Chambe J, Laib S, Hubbard J, et al. Floppy eyelid syndrome is associated with obstructive sleep apnoea: a prospective study on 127 patients. *J Sleep Res*. 2012;21:308–315.

16. Kadyan A, Asghar J, Dowson L, et al. Ocular findings in sleep apnoea patients using continuous positive airway pressure. *Eye*. 2010;24:843–850.
17. Rechtschaffen A, Kales A. *Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Publication No. 204*. Washington: U.S. Government Printing Office; 1968.
18. Zulauf M, Caprioli J, Boeglin RJ, et al. Number of stimuli as a reliability parameter in perimetry. *Ger J Ophthalmol*. 1992;1:86–90.
19. Bonomi L, Mrchini G, Marrafa M, et al. Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. *Ophthalmology*. 1998; 105:209–215.
20. Dielemans I, Vingerling JR, Wolfs RCW, et al. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology*. 1994;101:1851–1855.
21. Bengtsson B, Heijl A. A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. *J Glaucoma*. 2005;14:135–138.
22. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol*. 2008;53(suppl 1):S3–S10.
23. McNab AA. The eye and sleep. *Clin Experiment Ophthalmol*. 2005;33:117–125.
24. Waller EA, Bendel RE, Kaplan J. Sleep disorders and the eye. *Mayo Clin Proc*. 2008;83:1251–1261.
25. Séries F, Chakir J, Boivin D. Influence of weight and sleep apnea status on immunologic and structural features of the uvula. *Am J Respir Crit Care Med*. 2004;170: 541–546.
26. Schlötzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, et al. The pathogenesis of floppy eyelid syndrome. Involvement of matrix metalloproteinases in elastic fiber degradation. *Ophthalmology*. 2005;112:694–704.

ESTUDIO 3

Muniesa et al.

7.1 HIPÓTESIS

En el SPL existen unos cambios estructurales adicionales que pueden afectar a la biomecánica corneal de estos pacientes.

7.2 OBJETIVO

Determinar las propiedades biomecánicas de los pacientes con SPL mediante el Analizador de Respuesta Ocular (ORA) y compararlas con pacientes sin SPL.

7.3 METODOLOGÍA

Los pacientes fueron incluidos y evaluados secuencialmente desde Enero a Diciembre de 2012 en el Hospital Universiario Arnau de Vilanova de Lleida. Se incluyeron 107 pacientes de los cuales 37 tenían SPL y 70 sin SPL en los que se determinaron las propiedades biomecánicas de la córnea mediante el ORA. El estudió incluyó un total de 208 ojos (72 ojos con SPL y 136 sin SPL). Debido a la importante asociación entre el SPL y el SAHS, todos los pacientes incluidos habían sido previamente evaluados para descartar SAHS en la Unidad del Sueño del Hospital Universitario Arnau de Vilanova y Hospital Santa María de Lleida. El protocolo y consentimiento informado había sido aprobado por el Comité de Ética de nuestro hospital. Todos los pacientes incluidos firmaron el consentimiento informado.

El diagnóstico de SAHS se basó en una polisomnografía convencional o un estudio de sueño cardio-respiratorio. El diagnóstico de SAHS y la determinación de la severidad del mismo se hizo mediante el IAH. Se consideró SAHS leve cuando el IAH estaba entre 10 y 20h^{-1}, moderado cuando estaba entre 20 y 30h^{-1}, y severo cuando el IAH>30h^{-1}.

El estudio oftalmológico incluía: la agudeza visual corregida, la refracción, examen del polo anterior en lámpara de hendidura y fundoscopía, PIO medida con tonometría de aplanación de Goldmann, topografía corneal (TMS 4 Tomey), campimetría automática computerizada (Humprey - programa SITA-estándar; test 24/2) y medida del grosor de la capa de fibras nerviosas de la retina mediante tomografía de coherencia óptica (Stratus OCTm Carl Zeiss Ophthalmic Systems Inc.). La determinación del grosor corneal central (GCC) se realizó mediante un paquímetro ultrasónico (Ocuscan RXP Alcon) previa instilación de anestésico tópico y repitiendo la medida tres veces en cada ojo. La media de cada ojo fue considerada para el análisis.

El examen palpebral fue realizado específicamente para evaluar la laxitud palpebral y diagnosticar el SPL. El SPL se definió en base a la presencia de unos párpados superiores fácilmente evertibles con la tracción manual asociados a conjuntivitis papilar crónica (9).

No se incluyeron en el estudio pacientes con glaucoma ni con queratocono.

ANALIZADOR DE RESPUESTA OCULAR (ORA®)

El ORA analiza la deformación de la córnea tras un impulso de aire proporcionando información sobre las propiedades viscoelásticas de la misma. El ORA mide los cambios en la PIO entre dos sucesivos impulsos de aire que provocan la aplanación de la córnea. Los principales parámetros de biomecánica corneal determinados por el ORA son la histéresis corneal (HC) y el factor de resistencia corneal (FRC). La HC es indicativa de las propiedades viscosas de la córnea y refleja la capacidad del tejido corneal de absorber y disipar energía; le FRC es indicador de la resistencia a la deformación de la córnea. Aunque la HC y el FRC están relacionados, puede diferir significativamente y aportar información diferenciada de las propiedades biomecánicas de la córnea. El ORA también mide la PIO con compensación corneal (PIOcc) que minimiza la influencia del grosor corneal en la medida de la PIO, y la PIO Godlmann (PIOg) que equivale a la PIO tomada con el tonométro de aplanación de Goldmann. Dos medidas consecutivas con el ORA fueron obtenidas de cada ojo, pero sólo las lecturas de buena calidad determinadas por el mismo dispositivo ORA fueron tenidas en cuenta para el análisis.

ANÁLISIS ESTADÍSTICO

Los resultados se expresaron en medias ± DS. Se usaron modelos univariables para evaluar las diferencias en las propiedades biomecánicas corneales y demás parámetros entre los pacientes con SPL y sin SPL. El análisis de las variables demográficas se realizó mediante el test de la *t* de Student. Se usó el test de Mann-Whitney para analizar los datos entre grupos. Se construyeron modelos multivariables para evaluar las diferencias entre los parámetros de biomecánica corneal en pacientes con SPL y sin SPL, ajustando las diferencias a la edad y al IAH. Una $p < 0.05$ fue considerada estadísticamente significativa.

7.4. PRINCIPALES RESULTADOS

Se incluyeron un total de 208 ojos: 72 ojos con SPL y 136 sin SPL, correspondientes a 107 pacientes: 37 pacientes con SPL y 70 pacientes sin SPL. Los pacientes con SPL tenían significativamente mayor edad e IAH; no se diferenciaron significativamente respecto al IMC o el género.

1. La HC fue estadísticamente más baja en pacientes con SPL (9.51 ± 1.56) comparándola con pacientes sin SPL (11.66 ± 9.11) con una $p < 0.001$; tras ajustar los resultados a la edad y al IAH las diferencias continuaron siendo estadísticamente significativas ($p = 0.028$).

2. El FRC en pacientes con SPL fue de 10.02 ± 2.08 y en el grupo de pacientes sin SPL fue de 11.21 ± 5.36 ($p = 0.001$); pero tras ajustar a la edad y al IAH, se perdía la significación estadística ($p = 0.26$).

3. La PIOcc fue de 17.7 ± 4.8 en los pacientes con SPL y de 16.3 ± 4.4 en los pacientes sin SPL ($p = 0.036$); tras ajustar a la edad y al IAH, las diferencias no fueron estadísticamente significativas ($p = 0.87$).

4. No hubo diferencias en la PIOg ni en el GCC entre los dos grupos.

Tabla 7.1. Categorización de los pacientes sin SPL y con SPL según las variables clínicas.

	Pacientes sin SPL	Pacientes con SPL	P
Pacientes, n	70	37	
Edad, años	56±10	66±7	0.000
Sexo, masculino	78.7%	84.7%	0.293
IMC (kg/m^2)	30.52±4.62	32.11±6.06	0.067
IAH (h^{-1})	30.42±24.29	40.09±27.98	0.02 (0.018*)

*Ajustado a la edad.

Tabla 7.2. Variables de biomecánica corneal en pacientes sin SPL y con SPL.

	Sin SPL	Con SPL	P
ojos, n	136	72	
PIOcc (mm Hg)	16.3±4.4	17.7±4.8	0.036 (0.87*)
PIOg (mm Hg)	16.4±4.6	16.4±4.9	0.949
GCC (um)	551±36	548±29	0.525
HC (mm Hg)	11.66±9.11	9.51±1.56	<0.001 (0.028*)
FRC (mm Hg)	11.21±5.36	10.02±2.08	0.001 (0.26*)

*Ajustado a la edad y al IAH.

Corneal Biomechanical Properties in Floppy Eyelid Syndrome

MªJesús Muniesa Royo, MD,† Ana March de Ribot, MD,*† Manuel Sánchez-de-la-Torre, PhD,†‡ Valetín Huerva Escanilla, MD,*† Carmen Jurjo Campo, MD,*† and Ferran Barbé Illa, MD†‡*

Purpose: To determine corneal biomechanical properties in patients with floppy eyelid syndrome (FES) and to compare them with eyes of controls.

Methods: This case–control study included 208 eyes (72 eyes with FES and 136 without FES) of 107 patients (37 patients with FES and 70 without FES). Patients underwent a complete clinical eye examination that included corneal biomechanical evaluation carried out with the Reichert Ocular Response Analyzer.

Results: Corneal hysteresis (CH), corneal resistance factor (CRF), central corneal thickness (CCT), Goldmann-correlated intraocular pressure (IOPg), and corneal-compensated intraocular pressure (IOPcc) were evaluated. Mean CH was significantly lower in patients with FES than in those without FES (9.51 ± 1.56 vs. 11.66 ± 9.11; $P < 0.001$). These results remained statistically significant after adjusting for age and apnea–hypoapnea index (AHI) ($P = 0.028$). Mean CRF was 10.02 ± 2.08 in the group of patients with FES and 11.21 ± 5.36 in the group of patients without FES ($P = 0.001$). Mean IOPcc was 17.7 ± 4.8 in patients with FES and 16.3 ± 4.4 in those without FES ($P = 0.036$). After adjusting for age and AHI, these differences in CRF and IOPcc were not statistically significant ($P = 0.26$ and $P = 0.87$, respectively). No statistically significant difference was found between patients with and without FES for Goldmann-correlated intraocular pressure or CCT.

Conclusions: Patients with FES had statistically lower CH values. Our findings suggest that corneal biomechanical properties could be changed in patients with FES, reflecting additional structural changes in FES.

Key Words: floppy eyelid syndrome, corneal biomechanical properties, corneal hysteresis, glaucoma, keratoconus, sleep apnea syndrome

(*Cornea* 2015;0:1–4)

Received for publication November 13, 2014; revision received January 10, 2015; accepted January 16, 2015.

From the *Ophthalmology Department, Arnau de Vilanova Universitary Hospital, IRB Lleida, Lleida, Catalonia, Spain; †Respiratory Department, Arnau de Vilanova-Santa María Universitary Hospital, IRB Lleida, Lleida, Catalonia, Spain; and ‡Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES), Madrid, Spain.

Supported by IRB Lleida, Lleida, Catalonia, Spain.

The authors have no conflicts of interest to disclose.

Reprints: MªJesús Muniesa Royo, MD, Ophthalmology Department, Arnau de Vilanova Universitary Hospital, 80 Avenue Alcalde Rovira Roure, Lleida 25198, Spain, IRBLleida, Catalonia, Spain (e-mail: mariajesus.muniesa@gmail.com).

Floppy eyelid syndrome (FES) is a frequently underdiagnosed disorder of unknown pathogenesis. It is characterized by lax upper eyelids, which are easily everted with minimal traction, and chronic papillary conjunctivitis of the upper palpebral conjunctiva. Since the initial description by Culberston and Ostler in 1981,[1] FES has been associated with systemic conditions, like obstructive sleep apnea (OSA),[2–8] and ocular conditions, such as glaucoma[2,3,9] and keratoconus.[4,10,11] It is unclear whether FES and these other conditions are causally associated or whether they merely share common risk factors or have a common pathophysiological cause.

The study of corneal biomechanical properties in FES could point to some of the characteristics present in other structures associated with FES, such as the cornea, which could explain the relationship between FES and other conditions.

The Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY) records inward and outward corneal applanation after delivering a metered collimated air pulse and provides an indication of the viscosity and elastic properties of the cornea. Corneal hysteresis (CH) and corneal resistance factor (CRF), which are the corneal biomechanical metrics given by the ORA, have been studied under different ocular conditions. CH is significantly lower in cases of keratoconus[12] and is associated with progressive deterioration of the visual field in cases of glaucoma.[13] Corneal biomechanical properties in FES have not been studied previously.

The aim of this study was to determine whether FES is associated with changes in corneal biomechanical properties to study any other structural changes associated with FES.

MATERIALS AND METHODS

The study is a case–control study in which patients were sequentially evaluated from January to December 2012. We included 107 patients (37 with FES and 70 without FES) who agreed to undergo an ophthalmologic examination to study corneal biomechanical properties using the Reichert ORA. The study included a total of 208 eyes (72 eyes with FES and 136 without FES). Because one of the most consistently reported associations with FES is that of OSA,[2–8] all the patients studied had been previously admitted for OSA evaluation at either the Arnau de Vilanova University Hospital or at the Santa Maria Hospital in Lleida, Spain. The protocol and informed consent procedures were approved by the Ethics Committee of Arnau de Vilanova

University Hospital, Lleida, Spain. Informed consent was obtained from all patients.

Each subject underwent a complete medical and ophthalmologic examination. Diagnosis of OSA was based on either a conventional polysomnography or a cardiorespiratory sleep study. Apnea–hypopnea index (AHI) was calculated according to the average number of episodes of apnea plus hypopnea per hour of sleep or recording time.

The ophthalmologic examination included the following: best-corrected visual acuity with a recording of the refractive correction; slit-lamp and funduscopic examinations; Goldmann applanation tonometry; corneal topography (TMS-4; Tomey, Erlangen, Germany), visual field analysis with a Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA; SITA-standard program, central 24-2 threshold test); and measurement of the thickness of the retinal fiber layer using optical coherence tomography (Stratus OCT; Zeiss Carl Ophthalmic Systems Inc, Dublin, CA). Topical anesthetic was applied to each eye before ultrasonic corneal pachymetry (Ocuscan RXP; Alcon Laboratories, Inc), which was performed 3 times on each eye. The average measurements for each eye were then considered for analysis. Two consecutive ORA measurements were obtained for each eye, but only good-quality readings, as defined by the manufacturer, were stored. Eyelid examination was conducted specifically to evaluate eyelid laxity and obtain an FES diagnosis. Severity of eyelid laxity was measured in the 4 lids by distraction and snapback tests. Ease of eversion of the upper lid was also evaluated. FES was defined on the basis of easily evertible lids and papillary conjunctivitis affecting the same upper eyelid, which is the clinical definition of FES.[1,8] Easy lid eversion was characterized by increased laxity in the upper lids, which were easily distorted and everted with minimal superolateral traction. All eyes with FES of the present study were included in the clinical definition of FES. Different grades of FES were included in this group. The results of eyelid examination were dichotomized for the purpose of analysis as FES present or FES absent (Fig. 1).

None of the patients included in the study had previously undergone any form of surgical intervention to their eyelids or had been subjected to ocular surgery. Patients with glaucoma were not included in the study. No patient included in the study had established diagnostic criteria of keratoconus confirmed by a complete ophthalmologic evaluation and corneal topography. We did not include an eye if it was the fellow eye of a patient with KCN.

Noncontact intraocular pressure (IOP) and corneal biomechanical properties were measured using the ORA, which determines corneal biomechanical properties using an applied force–displacement relationship.[14–17] The ORA measures changes in IOP between 2 successive air-impulse applanations of the cornea. CH is the difference between these 2 pressures during the inward and outward applanation events; it provides an indication of viscous damping in the cornea, reflecting the capacity of the corneal tissue to absorb and dissipate energy. The difference in pressure reflects a viscoelastic biomechanical property of the cornea and is determined by the viscoelastic properties of the corneoscleral shell.[18] CRF is a measure of the cumulative effect of both viscous and elastic resistance encountered by an air jet deforming the corneal surface; it is an indicator of the overall resistance of the cornea to deformation. Although CH and CRF are related, they may significantly differ and each provides different information about the cornea.[12] The ORA also calculates both corneal-compensated IOP (IOPcc) and Goldmann-correlated IOP (IOPg). IOPcc is a measurement of IOP that minimizes corneal influence, whereas IOPg is the Goldmann applanation tonometer measurement corresponding to this device. Patients were tested using the ORA by a trained physician who was not aware of the results of the eye examination.

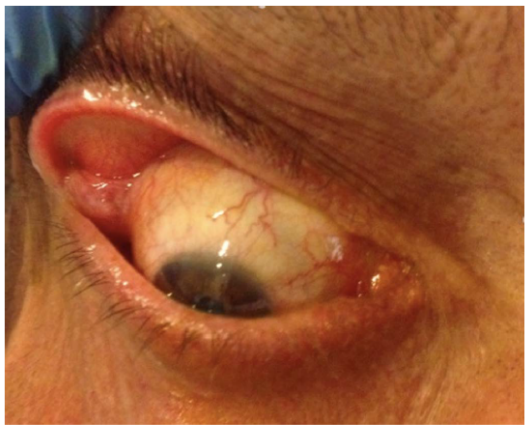


FIGURE 1. Floppy eyelid syndrome: defined on the basis of easily evertible lids and the presence of papillary conjunctivitis in the same upper eyelid.[1,8]

Statistical Analysis

Data were expressed as mean ± SD. We used univariable models to evaluate differences in corneal biomechanical properties and other parameters between patients with and without FES. Statistical analyses of the demographic data and ophthalmologic examinations were performed using an unpaired Student *t* test. We used a Mann–Whitney test to analyze data between groups. We built multivariable models to evaluate differences in corneal biomechanical parameters in FES versus non-FES while adjusting for differences in other parameters such as age and AHI. $P < 0.05$ was considered to be statistically significant. The language and environment for the R Foundation for Statistical Computing (Vienna, Austria) was used.

RESULTS

The study included a total of 208 eyes (72 eyes with FES and 136 without FES) of 107 patients (37 patients with FES and 70 without FES). A categorization of these patients based on the reported clinical findings is presented in Table 1. As expected, patients with FES were significantly older than

TABLE 1. Categorization of Patients Based on Reported Clinical Findings

	Non-FES Patients	FES Patients	*P*
Patients, n	70	37	
Age, mean ± SD, yr	56 ± 10	66 ± 7	<0.001
Gender, male	78.7%	84.7%	0.293
BMI, mean ± SD, kg/m^2	30.52 ± 4.62	32.11 ± 6.06	0.067
AHI, mean ± SD, h^{-1}	30.42 ± 24.29	40.09 ± 27.98	0.02 (0.018*)

*After adjusting for age and body mass index (BMI).
AHI indicates apnea-hipopnea index.

controls and had higher AHI, but there were no significant differences in gender or BMI. The results of a comparison of corneal biomechanical findings between patients with FES and the control group are given in Table 2. We adjusted the results obtained from the ORA parameters for age and AHI. Mean CH was significantly lower in patients with FES than in those without FES. These results remained statistically significant after adjusting for age and AHI. Although CRF and IOPcc were significantly lower in patients with FES than in controls, these differences were not statistically significant after adjusting for age and AHI. No statistically significant differences were found between patients with FES and in those without FES with respect to IOPg or CCT (Table 2).

DISCUSSION

In the present study, patients with FES had statistically lower CH values than patients without FES. Our findings therefore suggest that differences in corneal hysteresis between these 2 groups of patients reflected additional structural changes in FES. To the best of our knowledge, this is the first study to report corneal biomechanical properties in patients with FES.

Human corneal tissue is considered to be a viscoelastic material with measurable properties.[14–16] Luce[14] suggested that CH, determined using an ocular response analyzer, could serve as an independent in vivo indicator of corneal biomechanical measurement. Changes in CH may reflect structural changes in the ground substance of the cornea. ORA could provide invaluable information for delineating biomechanical conditions pertaining to the cornea.

TABLE 2. Categorization of Patients Based on Reported Corneal Biomechanical Findings

	Non-FES Patients	FES Patients	*P*
Eyes, n	136	72	
IOPcc, mm Hg	16.3 ± 4.4	17.7 ± 4.8	0.036 (0.87*)
IOPg, mm Hg	16.4 ± 4.6	16.4 ± 4.9	0.949
CCT, µm	551 ± 36	548 ± 29	0.525
CH, mm Hg	11.66 ± 9.11	9.51 ± 1.56	<0.001 (0.028*)
CRF, mm Hg	11.21 ± 5.36	10.02 ± 2.08	0.001 (0.26*)

*After adjusting for age and apnea-hipopnea index (AHI).
IOP indicates intraocular pressure; IOPcc, corneal-compensated IOP; IOPg, Goldmann-correlated IOP; CCT, central corneal thickness; CH, corneal hysteresis; CRF, corneal resistance factor.

Floppy eyelid syndrome is associated with ocular and systemic conditions such as glaucoma,[2,3,9] keratoconus,[4,10,11] and OSA.[2–8] The results of the present study suggest that more elastic or distensible ocular tissue may be associated with FES and that this may also help to explain the relationship between FES and other ocular pathologies such as glaucoma and keratoconus.

Corneal hysteresis has been associated with worsening of progressive visual field loss in cases of glaucoma.[13] It has also been reported that lower CH and CRF values may constitute a pressure-independent risk factor for glaucoma[19] and that CRF and CH values tend to be significantly lower in eyes with normal-tension glaucoma than in normal eyes.[20] Values for corneal biomechanical metrics have been reported to be statistically lower in patients with keratoconus than in healthy controls.[12,21,22] This is consistent with the hypothesis that corneal factors, such as lower corneal hysteresis, may constitute a risk factor for glaucoma and keratoconus in patients with FES; this could, in turn, be related to the composition of the eye wall itself. In patients with FES, the characteristics of the cornea, as part of the ocular globe, could perhaps be used to predict the characteristics of other ocular structures as the cribriform lamina. In patients with FES, lower CH values may constitute a risk factor for glaucoma due to an association with the response of the corneoscleral shell and the ocular vasculature to IOP-induced stress. It has also been recently published that patients with keratoconus tend to exhibit increased eyelid laxity.[23] Low CH values may offer clues to the association of FES with keratoconus and could provide evidence for an etiological hypothesis of keratoconus in FES. The results of the present study justify corneal biomechanical evaluation in patients with FES. It may provide additional valuable information for selecting qualified patients for refractive surgery.

We could speculate that the most severe cases of FES may be associated with major changes in corneal biomechanics. It is possible that the natural history of FES could be associated with progressive modifications of the corneal biomechanical properties reflected in CH. Further studies are needed to study this hypothesis.

One of the most consistently reported associations of FES is with OSA.[2–8] It has been observed that the uvula tissue taken from patients with OSA exhibits a loss of elastic fibers.[24] A pattern of elastic fiber depletion in tarsal connective tissue has also been reported in FES.[25] Culberston and Ostler[1] hypothesized a subtle alteration of the underlying generalized connective tissue being responsible for eyelid laxity in FES. The elastic fiber depletion described in FES and OSA could be indicative of some of the characteristics present in other structures[9] such as the cornea. It has been published that patients with keratoconus are at increased risk for sleep apnea.[26] The results of the present study, which reported lower corneal hysteresis in patients with FES than in the controls, would corroborate this hypothesis.

The difference in CCT between patients with FES and controls used for comparison in the present study was not statistically significant. This suggested that corneal hysteresis was affected by FES, regardless of CCT.

It has been published that aging can induce changes in corneal biomechanical properties,[16,27] and lower levels of corneal hysteresis in older patients have been observed.[16] The present study showed that patients with FES were significantly older than patients without FES and had increased AHI, suggesting that our subject sample provided a good reflection of what would be observed in the general population. This could also explain why the patients were not age and AHI matched with controls. After adjusting for age and AHI, CH was lower in patients with FES than in controls; this suggests that FES induces significant changes in corneal biomechanical properties, independent of age and AHI.

One limitation of our study was that we relied exclusively on corneal biomechanical properties as assessed by the ORA. Although this instrument has been widely used to provide estimates of corneal biomechanical properties, further studies are required to validate and compare ORA parameters with other methods of evaluating corneal biomechanical properties in FES to corroborate our results.

In conclusion, we found that FES was associated with significant changes in corneal biomechanical properties characterized by reduced corneal hysteresis; this, in turn, suggests that additional structural changes may be present in FES. Corneal hysteresis would help to explain associations between FES and other conditions, but further studies are needed to corroborate these results.

REFERENCES

1. Culbertson WW, Ostler HB. The floppy eyelid syndrome. *Am J Ophthalmol.* 1981;92:568–575.
2. McNab AA. Floppy eyelid syndrome and obstructive sleep apnea. *Ophthal Plast Reconstr Surg.* 1997;13:98–114.
3. Robert PY, Adenis JP, Tapie P, et al. Eyelid hyperlaxity and obstructive sleep apnea (O.S.A) syndrome. *Eur J Ophthalmol.* 1997;7:211–215.
4. Ezra D, Beaconsfield M, Sira M, et al. The associations of floppy eyelid syndrome: a case control study. *Ophthalmology.* 2010;117:831–838.
5. Muniesa MJ, Huerva V, Sánchez-de-la-Torre M, et al. The relationship between floppy eyelid syndrome and obstructive sleep apnoea. *Br J Ophthalmol.* 2013;97:1387–1390.
6. Chambe J, Laib S, Hubbard J, et al. Floppy eyelid syndrome is associated with obstructive sleep apnoea: a prospective study on 127 patients. *J Sleep Res.* 2012;21:308–315.
7. Mojon DS, Godlblum D, Fleichhauer J, et al. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. *Ophthalmology.* 1999;106:1182–1185.
8. Karger RA, White WA, Park WC, et al. Prevalence of floppy eyelid syndrome in obstructive sleep apnea-hypopnea syndrome. *Ophthalmology.* 2006;113:1669–1614.
9. Muniesa MJ, Sánchez-de-la-Torre M, Huerva V, et al. Floppy eyelid syndrome as an indicator of the presence of glaucoma in patients with obstructive sleep apnea. *J Glaucoma.* 2014;23:e81–e85.
10. Parunovic A, Ilic B. Floppy eyelid syndrome associated with keratotorus. *Br J Opthalmol.* 1988;72:634–635.
11. Donnefeld ED, Perry HD, Gibralter RP, et al. Keratoconus associated with floppy eyelid syndrome. *Ophthalmology.* 1991;98:1674–1678.
12. Fontes B, Ambrósio R, Jardim D, et al. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. *Ophthalmology.* 2010;117:673–679.
13. Congdon N, Broman A, Bandeen-Roche K, et al. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am J Ophthalmol.* 2006;141:868–875.
14. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg.* 2005;31:156–162.
15. Kamiya K, Hagishima M, Fujimura F, et al. Factors affecting corneal hysteresis in normal eyes. *Graefes Arch Clin Exp Ophthalmol.* 2008;246:1491–1494.
16. Kida T, Liu JH, Weinreb RN. Effects of aging on corneal biomechanical properties and their impact on 24-hour measurement of intraocular pressure. *Am J Ophthalmol.* 2008;146:567–572.
17. Sullivan-Mee M, Billingsley SC, Patel AD, et al. Ocular Response Analyzer in subjects with and without glaucoma. *Optom Vis Sci.* 2008;85:463–470.
18. Soergel F, Jean B, Seiler T, et al. Dynamic mechanical spectroscopy of the cornea for measurement of its viscoelastic properties in vitro. *Ger J Ophthalmol.* 1995;151–156.
19. Kaushik S, Pandy SS, Banger A, et al. Relationship between corneal biomechanical properties, central corneal thickness, and intraocular pressure across the spectrum of glaucoma. *Am J Ophthalmol.* 2012;153:840–849.
20. Morita T, Shoji N, Kamiya K, et al. Corneal biomechanical properties in normal-tension glaucoma. *Acta Ophthalmol.* 2012;90:48–53.
21. Hosseini A, Abolbashari F, Niyazmand H, et al. Efficacy of corneal tomography parameters and biomechanical characteristic in keratoconus detection. *Cont Lens Anterior Eye.* 2014;37:26–30.
22. Johnson RD, Nguyen MT, Lee N, et al. Corneal biomechanical properties in normal, forme fruste keratoconus, and manifest keratoconus after statistical correction for potentially confounding factors. *Cornea.* 2011;30:516–523.
23. Pihlblad MS, Schaefer DP. Eyelid laxity, obesity, and obstructive sleep apnea in keratoconus. *Cornea.* 2013;32:1232–1236.
24. Séries F, Chakir J, Boivin D. Influence of weight and sleep apnea status on immunologic and structural features of the uvula. *Am J Respir Crit Care Med.* 2004;170:541–546.
25. Schlötzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, et al. The pathogenesis of floppy eyelid syndrome. Involment of matrix metalloproteinases in elastic fiber degradation. *Ophthalmology.* 2005;112:694–704.
26. Saidel MA, Paik JY, Garcia C, et al. Prevalence of sleep apnea syndrome and high-risk characteristics among keratoconus patients. *Cornea.* 2012;31:600–603.
27. Elsheikh A, Wang D, Brown M, et al. Assessment of corneal biomechanical properties and their variation with age. *Curr Eye Res.* 2007;32:11–19.

ESTUDIO 4

Muniesa et al.

8.1 HIPÓTESIS

Los pacientes con SPL presentan alteraciones en la superficie ocular con cambios crónicos en el epitelio conjuntival que contribuyen a los signos y síntomas oculares que acompañan a los pacientes con SPL.

8.2 OBJETIVOS

1. Determinar el grado citológico en la clasificación de Nelson en la citología de impresión conjuntival de los pacientes con SPL y compararlos con pacientes sin SPL.

2. Determinar el grado de metaplasia escamosa en la citología de impresión conjuntival en los pacientes con SPL y compararlos con pacientes sin SPL.

8.3 METODOLOGÍA

Se incluyeron 82 ojos de 41 pacientes de forma consecutiva: 19 pacientes (38 ojos) diagnosticados de SPL bilateral en el Departamento de Oftalmología del Hospital Universitario Arnau de Vilanova de Lleida, y 22 pacientes (44 ojos) sin SPL (grupo control). El estudio se realizó a lo largo de 12 meses. El protocolo y el consentimiento informado había sido aprovado por el Comité de Ética de nuestro Hospital. Todos los pacientes incluidos firmaron el consentimiento informado.

Se recogió la historia médica y oftalmológica completa de todos los pacientes.

Los datos que se analizaron de cada paciente incluían la edad, el sexo, el IMC así como la presencia de enfermedades sistémicas y oculares. El examen mediante

lámpara de hendidura permitió la valoración de la reacción papilar conjuntival. La evaluación de los párpados condujo al diagnóstico de hiperlaxitud palpebral y SPL.

Todos los pacientes incluidos con SPL, se ajustaban a la definición clínica de SPL (9).

Ninguno de los pacientes incluidos era portador de lentes de contacto, usaba tratamiento tópico ocular de forma habitual, tenía signos de infección ocular activa o alergia ni había usado lágrimas artificiales en las 2 horas previas al screening.

CITOLOGÍA DE IMPRESIÓN CONJUNTIVAL

La citología de impresión conjuntival fue realizada en todos los pacientes y en ambos ojos, usando un papel de celulosa (Millipore; Billerica, Massachussetts, USA) capaz de adherir de una a tres capas de epitelio superficial. Este papel de filtro fue presionado sobre la conjuntiva tarsal y palpebral superior durante 5 segundos previa aplicación de anestésico tópico, siguiendo el método descrito por Egbert et al. (70). La muestras se fijaron en etanol 95º a 4ºC y se realizó tinción con ácido periódico de Shiff (PAS), y se estadió según la clasificiación de Nelson (71), basada en el tamaño celular, el tamaño del núcleo, el ratio núcleo-citoplasma de las células epiteliales no-secretoras y la densidad de células caliciformes (Figura 8.1).

Las células caliciformes son identificadas por la presencia de su material secretor mediante la tinción de PAS. La presencia de células caliciformes en la citología de impresión sólo se puede reconocer por la tinción PAS+ de su citoplasma. Se usó una clasificación de 0 a 3 para evaluar la presencia de metaplasia escamosa. El grado 0 hacía referencia a la ausencia de metaplasia y el grado 3 a metaplasia escamosa severa.

Tabla 8.1. Clasificación de Nelson (71).

Hallazgos	Grado 0	Grado 1	Grado 2	Grado 3
Tamaño célula	Pequeño	Pequeño	Grande	Grande
Citoplasma	Eosinófilo	Eosinófilo	Variable	Basófilo
Núcleo	Grande	Pequeño	Pequeño	Picnótico/ausente
Ratio núcleo-citoplasma	1:2	1:3	1:4 - 1:5	1:6
Células caliciformes/mm^2	> 500	350 – 500	100 - 350	<100
Citoplasma células caliciformes	PAS +++	PAS +++	PAS ++	PAS -

PAS: ácido periódico de Schiff

ANÁLISIS ESTADÍSTICO

Todos los resultados se expresaron como media ± DS. La media de los resultados de ambos ojos de cada paciente, fueron utilizados para el análisis. El test de Mann-Whitney fue utilizado para comparar los resultados entre ambos grupos. El *t*-test de Wilcoxon fue utilizado para analizar los resultados entre los ojos de cada paciente. El análisis de regresión lineal fue aplicado para estudiar la relación entre metaplasia/SPL y Nelson/SPL. Una regresión múltiple fue utilizada para ajustar los resultados a los posibles factores de confusión. Una $p < 0.05$ fue considerada como estadísticamente significativa.

8.4 PRINCIPALES RESULTADOS

El estudio incluyó 82 ojos de 41 pacientes: 38 ojos de 19 pacientes tenían SPL y 44 ojos de 22 pacientes sin SPL fueron utilizados como controles. Los pacientes con SPL eran significativamente mayores de edad y con IMC más alto que los controles. De modo que los resultados de la citología de impresión conjuntival se ajustaron a la edad y al IMC.

1. El grado en la clasificación de Nelson de los pacientes con SPL y en pacientes sin SPL fue de 1.89 ± 0.59 y 1.26 ± 0.42, respectivamente. Estas diferencias fueron estadísticamente significativas (p = 0.0014). Tras ajustar a la edad y al IMC, estas diferencias continuaron siendo signficativas (p = 0.0106).

2. El grado de metaplasia en el grupo con SPL fue de 1.41 ± 0.61 y en el grupo control fue de 0.75 ± 0.41; estas diferencias fueron estadísticamente significativas (p = 0.0003) manteniéndose significativas tras ajustar a la edad y al IMC (p = 0.0282).

Tabla 8.2. Categorización de los pacientes sin SPL y con SPL según las variables clínicas y citológicas.

	Grupo control sin SPL	Grupo con SPL	*P*
Pacientes, n	22	19	
Edad, años	46.59 ± 13.13	65.00 ± 8.69	0.001
Sexo, masculino	70.6%	76.5%	1
IMC (kg/m^2)	30.63 ± 5.50	35.32 ± 5.62	0.03
Grado de Nelson	1.26 ± 0.42	1.80 ± 0.59	0.0014 (0.0106)*
Grado de metaplasia	0.75 ± 0.41	1.41 ± 0.61	0.0003 (0.0282)*

*Ajustado a la edad y al IMC.

Evaluation of ocular surface changes in floppy eyelid syndrome by conjunctival impression cytology

(Submitted)

Mª Jesús Muniesa, MD,[1,2] Xavier Matias-Guiu, MD,[2,3] Manuel Sánchez-de-la-Torre, PhD,[2,4] Sara González,[2,3] Beatriz Vázquez,[1] Valentín Huerva, MD,[1,2] Montserrat Martínez, PhD,[2] Ferran Barbé, MD.[2,4]

[1] Department of Ophthalmology, Hospital Universitari Arnau de Vilanova, Lleida. Spain; [2] Institut de Recerca Biomèdica Lleida, Lleida, Spain; [3]Department of Pathology and Molecular Genetics, Hospital Universitari Arnau de Vilanova. Lleida. Spain; [4] Department of Pneumology. Hospital Universitari Arnau de Vilanova, Lleida, Spain. Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES), Madrid.

Corresponding author:

Mª Jesús Muniesa Royo

Department of Ophthalmology. Hospital Universitari Arnau de Vilanova. Lleida. Spain.

Av. Alcalde Rovira Roure, 80; 25198 Lleida. Spain.

Telephone number: +34649297040

mariajesus.muniesa@gmail.com

Financial support: Instituto de Salud Carlos III (FIS PS09/02224)

The sponsor/funding organization played no role in the design and conducting of this research.

Conflict of interest: No conflicting relationships exists for any authors.

Keywords: floppy eyelid syndrome, conjunctival impression cytology; ocular surface changes.

ABSTRACT

Purpose: To evaluate the ocular surface changes in floppy eyelid syndrome (FES) by comparing impression conjunctival cytological features between patients with floppy eyelid syndrome (FES) and normal controls.

Design: Case-control series.

Methods: Eighty-two eyes of 41 patients were included: thirty-eight eyes of 19 patients had FES and forty-four eyes of 22 patients did not as a control group. Conjunctival impression cytology specimens were taken from all the eyes studied and graded according to the Nelson system, based on cell size, nuclear size, nuclear-cytoplasmic ratio (N:C) in nonsecretory epithelial cells, and density of goblet cells. A classification from 0 to 3 was used to evaluate the grade of squamous metaplasia. FES was defined by easy upper eyelid eversion and tarsal papillary conjunctivitis.

Results: The mean Nelson grades obtained for the FES patients were 1.80 $\pm$ 0.59 and 1.26 $\pm$ 0.42 for the control group ($p = 0.0014$); when adjustments were made for age and body mass index (BMI), this significance remained ($p = 0.0106$). The mean metaplasia grades were 1.41 $\pm$ 0.61 in the FES group and 0.75 $\pm$ 0.41 ($p = 0.0003$) in the control group; these results remained statistically significant after adjusting for age and BMI ($p = 0.0282$).

Conclusion: Patients with FES were significantly more likely to exhibit abnormal conjunctival cytology characterized by a decrease in the number of goblet cells and an increase in squamous metaplasia.

INTRODUCTION

Floppy eyelid syndrome is an often underdiagnosed disorder that is characterized by lax upper eyelids that are easily distorted and everted with minimal traction; it is also associated with chronic papillary conjunctivitis of the upper palpebral conjunctiva.[1,2] FES was first described by Culbertson and Ostler in 1981[1] in overweight male patients who experienced nocturnal eyelid eversion caused by severe eyelid laxity. This condition produces significant ocular morbidity. Patients with FES present unilateral or bilateral ocular symptoms that range from occasional redness and irritation to tearing and foreign body sensations, mucoid discharge, dry eyes, photosensitivity, blurred vision, eyelid swelling, and corneal ulcer.[3,4] Ocular irritation leads to rubbing of the eyes which, in turn, increases ocular inflammation and worsens the initial situation. Non-surgical treatments include the administration of lubricating eye drops and the taping or shielding of the eyelids. In many patients, the chronic symptoms are resistant to medical therapy. In some cases, surgical shortening of the upper eyelid can be used to avoid nocturnal eversion.[5]

Objective evaluation and monitoring chronic changes in the ocular surface in FES are difficult. We propose conjunctival impression cytology to study ocular surface in FES patients. Impression cytology is a valuable tool for understanding ocular surface disorders.[6] It is a non-invasive technique that allows the determination of goblet cell characteristics and of the grade of squamous metaplasia in the most superficial layers of the conjunctival epithelium.[7] Impression cytology has been used in the evaluation of ocular surface diseases such as keratoconjunctivitis sicca,[8] vitamin A deficiency,[9] cicatricial pemphigoid,[10] atopic disease,[11] vernal keratoconjuctivitis,[12] and the effect on these of various therapies. To the best of our knowledge, there is only one previous study in which FES patients were examined by impression cytology both before and after surgery, but they did not compare the cytology features with non-FES patients.[5]

The aim of the present study was to determine the changes in conjunctival epithelium in patients with FES by impression cytology compared with patients without FES.

MATERIAL AND METHODS

Eighty-two eyes of 41 patients were consecutively included in the study. We recruited 19 patients (38 eyes) diagnosed with bilateral FES by the Oculoplastic Unit of the Arnau de Vilanova University Hospital in Lleida, Spain, and 22 patients (44 eyes) without FES (control group). The study was performed over 12 months. None of the patients included wore contact lenses, used topical eye medication, had had a previous ocular injury, had a history of allergic ocular disease, had any active infection of the eye, showed evidence of any systemic disease known to affect tear production, had had refractive surgery, and had used artificial tears within two hours of screening.

Both the protocol and informed consent were approved by the Ethical Committee of our hospital and written informed consent was obtained from each patient.

The data collected about each patient included age, sex, body mass index (BMI - calculated as BMI = weight (kg)/height squared (m^2)) and any associated systemic and ocular diseases. Slit-lamp examination was carried out to check for tarsal papillary reaction. Eyelid examination was conducted specifically to evaluate eyelid laxity and obtain a FES diagnosis. Horizontal distraction from the globe was assessed as described by Iyengar and Khan[13] and measured in millimetres. Lid distraction >5 mm for upper lids and >6 mm for lower lids was considered as significant and indicative of increased laxity.[14] FES was defined on the basis of easily evertible lids and papillary conjunctivitis affecting the same upper eyelid, which is the clinical definition of FES.[1] Easy lid eversion was characterized by increased laxity in the upper lids, which were easily distorted and everted with minimal supero-lateral traction.[15] All eyes with FES of the present study were included in the clinical definition of FES.

Conjunctival Impression Cytology

Impression cytology was performed on all of the patients, and on both their eyes, using a Millipore (Billerica, Massachusetts, USA) mixed cellulose ester filter to peel away one to three layers of superficial epithelial cells. Filter paper was pressed onto the superior tarsal and bulbar conjunctiva for 5 seconds after the previous application of topical anaesthesia, following the method described by Egbert et

al.[16] Samples were kept in 95º ethanol at +4ºC, stained with periodic acid Schiff (PAS), and graded according to the Nelson procedure,[17] based on cell size, nuclear size, the nuclear-cytoplasmic ratio (N:C) in non-secretory epithelial cells, and the density of goblet cells (see **Table 1**). Nelson grading system does not include the study of inflammatory cells.[17] Goblet cells have been identified by the presence of their secretory product using staining with PAS. The presence of goblet cells in impression cytology was only recorded when they appeared with PAS positive cytoplasm. We used a classification from 0 to 3 to evaluate the grade of squamous metaplasia observed in our cytology specimens. Grade 0 referred to an absence of squamous metaplasia, grade 1 to occasional squamous metaplasia, grade 2 to a moderate occurrence, and grade 3 to severe squamous metaplasia. Cell morphology was viewed under a light microscopy at 40× by a pathologist blinded to the result of the eyelid examination. Images were captured using a digital camera system. (**Figure 1-3**).

Statistical analysis

All the data were expressed as means ± standard deviation. As all FES patients had bilateral FES, data for both eyes were averaged for comparisons between the FES and control groups. The Mann-Whitney test was employed to compare data between the two groups. The Wilcoxon paired **t**-test was used to analyse data between the eyes of each subject. Linear regression analysis was applied to study the relationship between metaplasia/FES and Nelson/FES. Multiple regression analysis was performed to adjust results for variables that presented statistically significant differences between the group of FES patients and the controls. $P < 0.05$ was considered statistically significant. The language and environment for Statistical Computing R has been used.[18]

RESULTS

The study included 82 eyes of 41 patients. Thirty-eight eyes of 19 patients had FES and the 44 eyes of 22 patients without FES were used as control group. The patients were classified based on reported clinical findings including such parameters as age, gender, and BMI (see **Table 2)**. As expected, the subjects with

FES were significantly older and had higher BMIs than the control patients. There was no significant difference based on gender. We therefore adjusted the results obtained from the impression cytology scores for age and BMI.

The mean conjunctival impression cytology scores of the FES patients and controls according to the Nelson grading system and to the observed grade of squamous metaplasia are presented in **Table 2**. The mean Nelson grades obtained for the FES and control group patients were 1.89 $\pm$ 0.59 and 1.26 $\pm$ 0.42, respectively. This difference was statistically significant ($p = 0.0014$). When adjustments were made for age and BMI, this significance remained; the coefficient for Nelson grade/ FES versus non-FES was 0.73 with 95% confidence intervals (CI) of 0.19 and 1.29 and a p-value of 0.0106 (**Table 3**). The mean metaplasia grade in the FES group was 1.41 $\pm$ 0.61 and in the control group it was 0.75 $\pm$ 0.41; the difference was statistically significant ($p = 0.0003$). These results remained statistically significant after adjusting for age and BMI, with a coefficient for metaplasia grade/ FES versus non-FES of 0.66 and a 95% CI of 0.08 and 1.23 and a p-value of 0.0282 (**Table 4**).

DISCUSSION

In the present study, patients with FES presented significative changes in their conjunctival epithelium compared with controls. These changes were a loss of goblet cells and an increase in squamous metaplasia. To the best of our knowledge, this study remains the first to report conjunctival epithelial changes in patients with FES by impression cytology compared them with patients without FES. A previous report by Medel et al[5] was based on a study of 16 patients (including 26 eyelids) with FES, in which the patients were examined by impression cytology both before and after surgery. They showed a postoperative improvement in cytology after FES surgery, but they did not compare the cytology features with non-FES patients. The present study features the largest cohort of FES patients that has been used to study the ocular surface by impression cytology.

Many disorders, such as atopic dermatitis, cicatricial pemphigoid, Steve-Johnson syndrome, severe chemical injures, dry eye and trachoma, have been associated with squamous metaplasia and a decreased number of goblet cells. [19] The present study provided objective findings to support that excessive eyelid laxity causes a

clinical condition characterized by chronic changes in conjunctival epithelium such as squamous metaplasia and loss of goblet cells.

As a result of the loss of goblet cells and the abnormalities in epithelial differentiation exhibited by FES eyes, the tear-film could become unstable, secondary to a reduction in the thickness of its mucin layer. In the absence of mucin, the corneal epithelial cells are hydrophobic and therefore cannot be wetted by aqueous tears.[20] Reduced numbers of filled goblet cells, identified by PAS staining, has long been associated with dry eye syndrome and ocular surface inflammation. Squamous metaplasia are the result of a process of abnormal epithelial differentiation: in other words, it is produced by the pathological transition from a non-keratinised, stratified (secretory or nonsecretory) epithelium (such as conjunctival epithelium) to a non-secretory keratinised epithelium; this has been associated with chronic irritation of the type that occurs in FES.[21] There have also been reports of elevated tear film osmolarity being associated with a reduced number of filled conjunctival goblet cells.[22] Studies of tear osmolarity could help to improve our understanding of changes in the ocular surface in FES patients.

This study showed the alterations in the conjunctival epithelium in patients with FES assuming that the causes that lead to these changes are multiple, and include a mechanical trauma that occurs due to the nocturnal lid eversion, a dysfunction of the tear and meibomian glands, a poor lid apposition, and damage to the eyelid skin.[3,23] Some of the patients were noted to have slept with the eyelid everted against their pillow and many had associated corneal abnormalities and severe discomfort. Meibomian gland dysfunction causes evaporative tear deficiency due to hyposecretion of lipids in tears and destabilization of the tear film; in turn, this instability is responsible for dry eye symptoms.[22,24,25] FES lid skin also characteristically exhibits high temperatures, high water evaporation rates and hyperpigmentation.[3] In our series, FES mainly affected men with high BMIs, as described in the first report on this syndrome.[1] FES, associated with a high body mass index and obstructive sleep apnea, should be suspected in any obese patients with chronic red and tearing eyes.[4, 26] Hypoxia during sleep can not only cause floppy eyelids but can also conceivably cause damage to the eyelid skin by ischemia-reperfusion injury. As a result, the skin becomes chronically inflamed,

leading to an increase in its temperature and the loss of the normal barrier against water evaporation.

The limitations of this study include possible referral bias in the populations studied. Our study demonstrated that patients with FES were significantly older and had higher BMIs than those without FES; this suggests that our subject sample provided a good reflection of what would be observed amongst the general population of FES. This could also explain why the subjects were not well-matched with the controls for age and BMI. After adjusting for age and BMI, the Nelson and metaplasia grades were higher in patients with FES than in control patients; this suggests that FES induces significative changes in conjunctival impression cytology. The relationship between the Nelson grade and the presence or absence of FES continued to be significant, however, age was a confounding factor, but its effect was not superior to that of FES when explaining differences in Nelson grades. As age was not significant, but had a confounding effect, the influence of FES on the Nelson grade for young people was greater than in the older age cohorts. After adjusting for age and BMI, the relationship between FES and metaplasia continued to be both significant and of the same magnitude. These results therefore suggest that FES patients display a higher degree of metaplasia and loss of goblet cells than those without FES, independently of age or BMI.

While there are numerous clinical and research applications of impression cytology, it has not yet become a routine diagnostic tool in most clinics because it is relatively cumbersome and time consuming for both clinician and pathologist. However, the ability to obtain multiple samples of the ocular surface at one sitting with minimal discomfort to the patient makes it an ideal method of investigating ocular surface disorders when the clinical diagnosis or the treatment response needs to be substantiated and documented.[27] In many patients with FES, the chronic symptoms are resistant to medical therapy. We suggested in the present study that FES is associated to significant chronic changes in conjunctival epithelium. So, we propose impression conjunctival cytology as a useful tool to quantify and monitor the ocular surface changes in FES. Impression cytology might help in the investigation of the pathogenesis of FES as well as for follow-up and therapy control.

In conclusion, the study of ocular surface by impression cytology provides an objective method to evaluate the ocular surface disorder in FES. Patients with FES presented significative changes in their conjunctival epithelium characterized by a loss of goblet cells and an increase in metaplasia. We considered that the changes in the ocular surface observed in this study were only part of a wider, multifactorial disease process. Further studies are needed to advance the study of ocular surface disorder in FES.

REFERENCES

1. Culbertson WW, Ostler HB. The floppy eyelid syndrome. Am J Ophthalmol 1981;92:568-75.
2. Culbertson WW, Tseng SC. Corneal disorders in floppy eyelid syndrome. Cornea 1994;13:33-42.
3. Tzong-Shyue D, Di Pascuale M, Gao Y, et al. Tear film dynamics in floppy eyelid syndrome. Invest Ophthalmol Vis Sci 2005;46:1188-1194.
4. Pham TT, Perry JD. Floppy eyelid syndrome. Curr Opin Ophthalmol 2007;18(5):430.
5. Medel R, Alonso T, Vela JI, et al. Conjunctival cytology in floppy eyelid syndrome: objective assessment of the outcome of surgery. Br J Ophthalmol 2009;93:513-517.
6. Singh R, Joseph A, Umapathy T, et al. Impression cytology of the ocular surface. Br J Ophthalmol 2005;89(12):1655-1659.
7. Lopin E, Deveney T, Asbell PA. Impression cytology: recent advances and applications in dry eye disease. Ocul Surf 2009;7(2):93-110.
8. Haller-Schober E, Schwantzer G, Berghold A, Fischl M, Theisl A and Horwath-Winter J. Evaluating an impression cytology grading system (IC score) in patients with dry eye syndrome. Eye (2006) 20, 927–933.
9. Wittpeen JR, Tsen SC, Sammer A. Detection of early xerophthalmia by impression cytology. Arch Ophthalmol 1996;104:237-9.
10. Nelson JD. Ocular surface impressions using cellulose acetate filter material: ocular pemphigoid. Surv Ophthalmol 1982:27:67-9.

11. Dogru M, Katakami C, Nakagawa N, et al. Impression cytology in atopic dermatitis. Ophthalmol 1998;105:1478-84.
12. Aragona P, Romeo G, Puzzolo D, et al. Impression cytology of the conjunctival epithelium in patients with vernal conjunctivitis. Eye 1996;10:82-5.
13. Iyengar SS, Khan JA. Quantifying upper eyelid laxity in symptomatic floppy eyelid syndrome by measurement of anterior eyelid distraction. Ophthal Plast Reconstr Surg 2007;23:255.
14. Kadyan A, Asghar J, Dowson L, et al. Ocular findings in sleep apnoea patients using continuous positive airway pressure. Eye (London) 2010 May;24(5):843-50.
15. Ezra DG, Beaconsfield M, Sira M. et al. The Associations of Floppy Eyelid Syndrome: A Case Control Study. Ophthalmology 2010;117:831-838.
16. Egbert PR, Lauber S, Maurice DM. A simple conjunctival biopsy. Am J Ophthalmol 1977;84:798-801.
17. Nelson JD, Wright JC. Conjunctival goblet cell densities in ocular surface disease. Arch Ophthalmol 1984;102:1049-1051.
18. R Development Core Team (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL.
19. Calonge M, Yolanda D, Sáez V, et al. Impression cytology of the ocular surface review. Exp Eye Res 2004;78:457-72.
20. Karalezli A, Borazan M, Altinors D, et al. Conjunctival impression cytology, ocular surface, and tear-film changes in patients treated with systemic isotretinoin. Cornea 2009;28:46-50.
21. Dos Santos F, Domingues E, de Nadai J, et al. Impression cytology findings in bullous keratopathy. Br J Ophthalmol 2010;94:773-776.
22. Lemp M, Bron A, Baudiouin C, et al. Tear Osmolarity in the diagnose and management of dry eye disease. Am J Ophthalmol 2011;151(5):792-798.
23. Gonnering RS, Sonneland PR. Meibomian gland dysfunction in floppy eyelid syndrome. Ophthal Plast Reconstr Surg 1987;3:99-103.

24. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. Arch Ophthalmol 1995;113:1266-70.
25. Lee SH, Tseng SC. Rose Bengal staining and cytological characteristics associated with lipid tear deficiency. Am J Ophthalmol 1997;124:736-50.
26. Muniesa MJ, Huerva V, Sánchez-de-la-Torre M, et al. The relationship between floppy eyelid syndrome and obstructive sleep apnea. Br J Ophthalmol 2013;97(11):1387-90.
27. Singh R, Joseph A, Umapathy T, Tint NL, Dua HS. Impression cytology of the ocular surface. Br J Ophthalmol 2005;89:1655-1659.

Table 1. Nelson grading system.[17]

Findings	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Cell size	Smaller	Small	Large	Large
Cytoplasm	Eosinophil	Eosinophil	Variable	Basophil
Nucleus	Large	Small	Small	Picnotic/absent
Nuclear: cytoplasmic ratio	1:2	1:3	1:4-1:5	1:6
Goblet cells/mm²	>500	350-500	100-350	<100
Goblet cells cytoplasm	PAS+++	PAS+++	PAS++	PAS-

PAS: periodic acid-Schiff reagent.

Table 2. Categorization of FES patients and controls based on reported clinical findings and mean ± SD values of the conjunctival impression cytology scores.

	Control group	**FES group**	***P value***
N eyes	44	38	
Age (yrs)	46.59 ± 13.13	65.00 ± 8.69	0.001
Gender, male %	70.6	76.5	1
BMI (kg/m²)	30.63 ± 5.50	35.32 ± 5.62	0.03
Nelson grade	1.26 ± 0.42	1.80 ± 0.59	0.0014 (0.0106)*
Grade of metaplasia	0.75 ± 0.41	1.41 ± 0.61	0.0003 (0.0282)*

FES: floppy eyelid syndrome; BMI: Body mass index; * after adjusting for age and BMI.

Table 3. Nelson Grade according to the presence of FES. Results of the multivariate linear regression models used to measure the effect of FES, unadjusted and adjusted for age and BMI.

	Unadjusted model	Unadjusted model	Adjusted model	Adjusted model
	Coefficent[CI95 %]	p-value	Coefficient[CI95 %]	p-value
Constant	1.25[1.04,1.47]	<0.0001	1.93[0.54,3.33]	0.0083
FES	0.54[0.22,0.87]	0.0014	0.73[0.19,1.29]	0.0106
Age	-	-	-0.01[-0.03,0.00]	0.1294
BMI(kgr/m²);	-	-	0.00[-0.04,0.04]	0.98
R^2	23.0%		23.9%	

BMI: Body Mass Index; R^2: Coefficient of determination.

Table 4. Metaplasia Grade according to the presence of FES. Results of the multivariate linear regression models to measure the effect of FES, unadjusted and adjusted for age and BMI.

	Unadjusted model	Unadjusted model	Adjusted model	Adjusted model
	Coefficient[CI95 %]	p-value	Coefficient[CI95 %]	p-value
Constant	0.76[0.53,0.98]	<0.0001	1.05[-0.48,2.48]	0.1686
FES	0.66[0.33,0.99]	0.0003	0.66[0.08,1.23]	0.0282
Age	-	-	-0.00[-0.02,0.02]	0.9078
BMI(kgr/m^2);	-	-	-0.01[-0.05,0.03]	0.6914
R^2	29.9%		23.0%	

BMI: Body Mass Index; R^2: Coefficient of determination.

FIGURES LEGENDS

Figure 1. Conjunctival impression cytology: Nelson grade 0; Metaplasia grade 0.

Figure 2. Conjunctival impression cytology: Nelson grade 2; Metaplasia grade 2.

Figure 3. Conjunctival impression cytology: Nelson grade 3; Metaplasia grade 3.

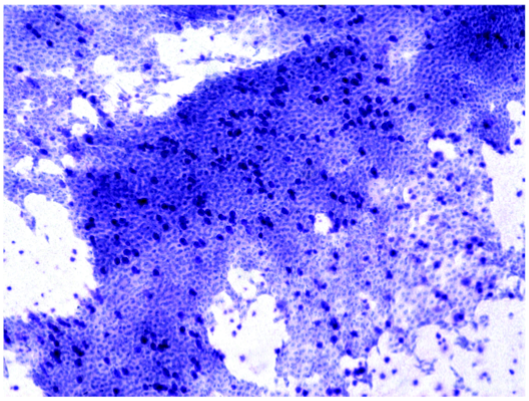


Figure 1

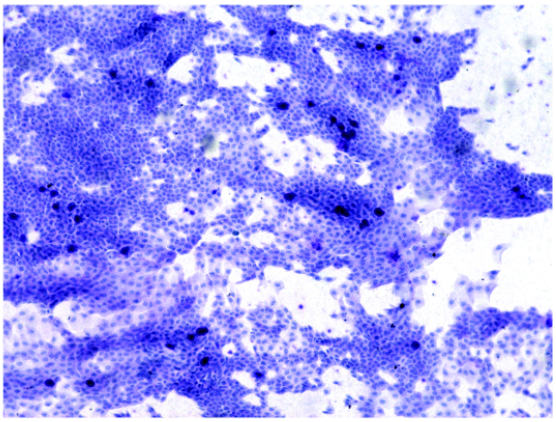


Figure 2

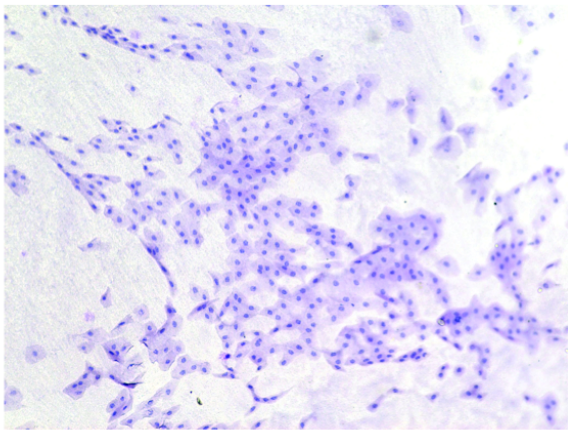


Figure 3

DISCUSIÓN

La presente tesis doctoral tiene dos partes diferenciadas. Por un lado analiza la relación entre el SAHS y las dos patología oculares que de forma más importante han sido relacionadas con el SAHS, como son el SPL y el glaucoma. Con este objetivo, se han presentado los artículos 1 y 2. Por otro lado, se han analizado aspectos específicos del SPL como son la biomecánica corneal y los cambios citológicos de la superficie ocular de los pacientes con SPL. Con este objetivo se han presentado los estudios 3 y 4.

En el primer estudio, la incidencia de hiperlaxitud palpebral fue significativamente más alta en los pacientes con SAHS que en los pacientes sin SAHS y estas diferencias siguieron siendo significativas tras ajustar a la edad y al IMC. Estos resultados sugieren que el SAHS podría ser un factor de riesgo independiente para la hiperlaxitud palpebral. Sin embargo, la prevalencia de SPL en los pacientes con SAHS no fue diferente estadísticamente, a pesar de que la prevalencia de SPL entre los pacientes con SAHS severo alcanzó el 20%. Según la bibliografía revisada, el presente trabajo representa el estudio con un tamaño muestral mayor de pacientes con SPL (n = 45) en los que se ha realizado un estudio para descartar SAHS mediante PSG, que es la prueba de referencia internacional para el diagnóstico de SAHS (72). Entre los pacientes con SPL, la prevalencia de SAHS alcanzó el 85% y la mayoría de ellos tenían SAHS severo. Esta prevalencia contrasta con la prevalencia de SAHS en la población general estimada entre el 2% y el 5% en edades medias (54), y con la prevalencia de SAHS entre la población obesa estimada en el 40% (73). Por lo tanto, esta asociación entre el SAHS y el SPL parece ser no sólo un epifenómeno. McNab (53) reportó un serie de 50 pacientes con SPL de los cuales 48 (96%) tenían historia de alteraciones respiratorias en el sueño, y 26 de los 27 pacientes en los que se realizó una PSG, fueron confirmados con el diagnóstico de SAHS. Ezra et al (54) estudiaron la presencia de SAHS en 102 pacientes con SPL usando el índice de somnolencia diurna de Epworth, que no es un método válido para diagnosticar SAHS.

La prevalencia del SPL en la población con SAHS varía en los diferentes estudios. Esta prevalencia varía del 2.2% al 32%, e incluye estudios de Robert et al (10), 1/46, 2.2%; Karger et al (52), 1/44, 2.3%; McNab et al (53), 3/20, 15%; kadyan et al (16), 28/89, 31.5%; Mojon et al (51), 14/44, 32%; y Chambe et al (15), 23/89, 25.8%. Un consenso no ha sido claramente alcanzado. Kadyan et al (16) usaron solamente oximetría, que no es un método válido para el diagnóstico de SAHS, McNab et al (53) tenían un muestra muy pequeña de pacientes con SPL y Monjon et al (51) no ajustaron los resultados a la edad ni al IMC. Karger et al (52) usaron la PSG para el diagnóstico de SAHS y encontraron una asociación entre la fácil eversión palpebral y el SAHS cuando estudiaron a 15 pacientes sin SAHS y a 44 pacientes con SAHS, pero sus hallazgos perdían significación estadística cuando ajustaban los resultados a la edad y al IMC. Nuestros resultados son comparables a los de Chambe et al (15) con 89 pacientes con SAHS diagnosticados mediante poligrafía nocturna y 38 pacientes sin SAHS, en los cuales la prevalencia de SPL fue del 15.8% en los pacientes sin SAHS y del 25.8% en la población con SAHS (diferencias no estadísticamente significativas), con una significante correlación entre la severidad del SAHS y el SPL y la laxitud palpebral. Por lo tanto, el presente estudio figura entre los estudios con mayor tamaño muestral de pacientes con SAHS no tratados con CPAP diagnosticados mediante un método considerado válido para detectar SAHS, en los cuales se ha descartado la presencia de SPL.

Nuestros resultados sugieren que el SAHS podría representar un subconjunto de condiciones relacionadas con la hiperlaxitud palpebral, y a partir de cierto umbral de hiperlaxitud, los pacientes correrían el riesgo de desarrollar el SPL con alteraciones a nivel de la conjuntiva, de la córnea y de la película lagrimal (73). El SAHS se ha sugerido como una posible causa de SPL en un estudio que mostró como el SPL podría resolverse simplemente con el uso de CPAP (55).

Hay diferentes hipótesis etiológicas sobre la asociación entre el SPL y el SAHS. En su descripción inicial, Culberston y Ostler propusieron que el trauma mecánico repetido era el causante de la conjuntivitis papilar, pero no ofrecían una hipótesis para explicar la elasticidad asociada. Netland et al (74) fueron los primeros en destacar anormalidades en las fibras elásticas, describiendo una disminución a nivel de la elastina tarsal. Sin embargo, no está claro si esta depleción en las fibras elásticas es causal o secundaria. Schlotzer-Schrehardt et al (59) demostradon una

sustancial pérdida del fibras elásticas y cambios ultraestructurales en las fibras residuales, junto con una sobreexpresión de enzimas elastolíticas en el tarso y en la piel de los pacientes con SPL. Estos cambios en las fibras elásticas son de particular interés para aquellos que proponen la relación entre el SPL y el SAHS. Se ha observado en los tejidos de la úvula de los pacientes con SAHS sometidos a úvulofaringoplastia una pérdida de fibras elásticas (10,74,75). Estos cambios podrían explicar como el SAHS, la hiperlaxitud palpebral y el SPL pueden ser diferentes manifestaciones de una misma enfermedad. Los hallazgos en nuestro estudio con una significante asociación entre la hiperlaxitud palpebral y el SAHS, parecen apoyar esta hipótesis sugiriendo que el SAHS podría contribuir a la alteración subyacente de los tejidos palpebrales. Por otro lado, la asociación entre el SPL y el SAHS ha estado influenciada de manera importante por la teoría de la isquemia-reperfusión. McNab (62) propuso que esta asociación podría explicar la relación entre la postura al dormir y la presión ejercida sobre el ojo, exacerbada por la hipoxia, induciendo isquemia-reperfusión. Evidencia previa sugiere la asociación con el sueño ya que el SPL es frecuentemente más sintomático en el lado del que duerme el paciente (76). Pero esta asociación no es exacta, como hemos visto en el presente estudio, quitando apoyo a la teoría mecánica.

Los clínicos deben tener en cuenta la asociación entre el SPL y el SAHS ya que el SAHS puede detectarse en pacientes con SPL, y los especialistas en sueño pueden ser los primeros en detectar síntomas oculares de SPL en pacientes con diagnóstico de SAHS. El presente estudio confirma que el SAHS es muy frecuente entre los pacientes con SPL pero que el SPL no es tan común entre la población general con SAHS.

En el segundo estudio se detectó una alta prevalencia de glaucoma entre los pacientes con SAHS que también tenían SPL (23.07%) sugiriendo que el SPL podría ser un importante marcador de glaucoma entre los pacientes con SAHS. La asociación entre SAHS y glaucoma ha sido sugerida en varios estudios. Sin embargo, la prevalencia de glaucoma en la población con SAHS y con SPL como posible marcador de glaucoma ha sido poco estudiada previamente : McNab (53) estudió una pequeña muestra sin incluir un grupo control de pacientes con SAHS pero sin SPL. Robert et al (10) no determinó cuales de los pacientes con glaucoma

tenían SAHS. Otros estudios publicados han mostrado la prevalencia de glaucoma en pacientes con SAHS sin tener en cuenta la presencia de SPL. Geyer et al (12) reportó que la prevalencia de glaucoma en la población SAHS era similar a la encontrada en la población general caucásica (63,64): un 2% de prevalencia de glaucoma en pacientes con SAHS diagnosticados mediante PSG (5/228). Kadyan et al (16) reportó que la prevalencia de GPAA en pacientes con SAHS (3/89, 3.4%) era similar a la de la población general (2%). En 2007, Sergi et al (13) reportaron 3 de 51 pacientes con SAHS (5.9%) con GNT; esto sugería que la prevalencia de GNT en los pacientes con SAHS era superior a la esperada en una población caucásica de la misma edad y que el SAHS podía ser un factor de riesgo importante para el GNT. Un estudio más reciente de Chambe et al (15) mostró que la prevalencia de glaucoma en pacientes con SAHS diagnosticados medante poligrafía respiratoria nocturna era del 5.6% (5/89). En 2010, Lin et al (14) reportó una prevalencia del 5.7% de GNT entre pacientes con SAHS (12/209) pero ningún paciente con glaucoma entre 38 pacientes sin SAHS. Monjon et al (11) encontraron una prevalencia del 7.2% de glaucomas entre 69 pacientes con SAHS diagnosticados mediante PSG (5/69), lo cual sugiere una fuerte asociación entre glaucoma y SAHS.

Nuestro estudio confirma la alta prevalencia de glaucoma entre los pacientes con SAHS publicada previamente, con un 12.9% de glaucoma entre todos los pacientes SAHS incluidos en el presente estudio. Es posible que esta prevalencia sea superior a las publicaciones previas debido al gran número de pacientes con SPL incluidos en la muestra. Cuando nosotros excluimos los pacientes con SPL, la prevalencia de glaucoma entre la población con SAHS fue del 5.3%, y ésta no difería significativamente de la prevalencia de glaucoma en pacientes SAHS de estudios previos. Cuando incluíamos en el análisis solamente los pacientes con SAHS y con SPL, la prevalencia de glaucoma alcanzaba el 23% siendo significativamente superior a la prevalencia de glaucoma en la población SAHS publicada previamente. Estos resultados apoyan la hipótesis de que el SPL podría ser un indicador de glaucoma en los pacientes con SAHS. Por otro lado, se sabe que el glaucoma está relacionado con la edad y con el IMC (77,78). La diferencias observadas en la prevalencia de glaucoma entre pacientes con SAHS y con SPL y pacientes con SAHS pero sin SPL del presente estudio, se mantenían significativas tras ajustar los resultados a la edad y al IMC, sugiriendo que el SPL podría ser un

factor de riesgo de glaucoma en la población con SAHS. Además, la presencia de glaucoma no se relacionó con la severidad del SAHS definida por su IAH.

Por lo tanto, el SPL podría ser útil para identificar los individuos con mayor probabilidad de tener glaucoma entre los pacientes diagnosticados de SAHS. Nuevos estudios son necesarios para corroborar estos resultados y estudiar si el SPL es un factor de riesgo independiente de glaucoma en pacientes sin SAHS.

Debido al carácter observacional del estudio que presentamos, los resultados obtenidos no permiten extraer una conclusión sobre la relación causal entre glaucoma, SAHS y SPL. Diferentes estudios han propuesto la etiología vascular en el glaucoma (11,13). En pacientes con SAHS, los prolongados episodios repetidos de apneas durante el sueño van acompañados de hipoxia y de un aumento de la resistencia vascular compremetiendo la perfusión y la oxigenación de la cabeza del nervio óptico. Pero este compromiso vascular no justificaría el aumento de la PIO, de modo que no podemos excluir la posibilidad de que otros factores intervengan en el glaucoma de los pacientes con SAHS. Se sabe que en los pacientes obesos se produce un aumento de la PIO durante los cambios posicionales del cuello por compresión (68). Y tanto el SPL como el SAHS se asocian de forma independiente a la obesidad. Además, es posible que los cambios en las fibras elásticas descritas en pacientes con SPL (59) y con SAHS (61) pudieran indicar algunas de las características presentes en otras estructuras oculares como la lámina cribosa y/o la malla trabecular. Estos cambios podrían aumentar el riesgo de glaucoma en los pacientes con SAHS afectos de SPL. Más estudios son necesarios para corroborar esta hipótesis.

En el tercer estudio, los pacientes con SPL presentaron valores de histéresis corneal significativamente más bajos que los pacientes sin SPL. Nuestros resultados sugieren que las diferencias en la histéresis corneal entre estos dos grupos de pacientes podrían indicar cambios estructurales adicionales en el SPL. En la bibliografía revisada, no se han encontrado estudios previos sobre propiedades biomecánicas en pacientes con SPL.

El tejido corneal humano es considerado un material viscoelástico con propiedades medibles (79-81). Luce (79) sugerió que la HC, determinada por el ORA, podía ser un indicador *in vivo* de la biomecánica corneal. Cambios en la HC

pueden reflejar cambios estructurales en el tejido corneal. Por lo tanto, el ORA aportaría una información muy preciada para determinar las propiedades biomecánicas de la córnea.

Como se ha descrito previamente, el SPL se asocia con patologías oculares y sistémicas como el glaucoma (10,53), el queratocono (39,46,54) y el SAHS (10,15,51-54). Los resultados del presente estudio sugieren que un tejido ocular más elástico o distensible puede estar asociado al SPL y esto ayudaría a explicar la relación entre el SPL con otras patologías oculares como el glaucoma o el queratocono.

La HC ha sido asociada con empeoramiento progresivos del campo visual en pacientes con glaucoma (82). Se ha descrito que valores más bajos en la HC y en el FRC pueden ser factores de riesgo independientes de la PIO para el glaucoma (83) y que el FRC y la HC tienden a ser significativamente más bajos en el GNT que en los ojos sanos (84). En el queratocono también se han descrito valores de biomecánica corneal significativamente más bajos que en controles sin queratocono (85-87). Estos resultados previos apoyarían la hipótesis de que factores corneales, como la HC baja, podrían ser factores de riesgo de glaucoma y queratocono en pacientes con SPL; ésto a su vez, se relacionaría con la composición generalizada de los tejidos oculares. En los pacientes con SPL, las características de la córnea, como una parte del globo ocular, podrían ser utilizadas para predecir las características de otras estructuras oculares como la lámina cribosa. En los pacientes con SPL, valores de HC más bajos podrían ser un factor de riesgo de glaucoma debido a la asociación con la respuesta de la pared corneoescleral y la vasculatura ocular al estrés inducido por la PIO. Se ha publicado recientemente que los pacientes con queratocono tienden a presentar un aumento en la laxitud palpebral (17). Valores bajos de HC podrían ofrecer claves para explicar la asociación entre el SPL y el queratocono y proporcionar evidencia para una hipótesis etiológica común entre estas patologías.

Como se ha dicho previmente, una de las asociaciones más importantes del SPL, es el SAHS (10,15,51-54). Y los cambios a nivel de las fibras elásticas descritas en el tarso de los pacientes con SPL (59) y en la úvula de los pacientes con SAHS (61), podrían indicar cambios en otras estructuras como la córnea. Los resultados del

presente estudio, donde los valores de HC fueron significativamente más bajos en pacientes con SPL que en controles, podrían apoyar esta hipótesis.

Las diferencias en el grosor corneal central (GCC) entre pacientes con SPL y sin SPL, no fueron significativas en el estudio que presentamos, indicando que las diferencias encontradas en la HC, eran independientes del GCC.

Se ha publicado que la edad puede inducir cambios en la biomecánica corneal con valores más bajos en los pacientes de más edad (81,88). Tras ajustar los resultados a posibles factores de confusión como la edad y el IAH, la diferencias en la HC de nuestro estudio, se mantenían significativas entre pacientes con y sin SPL, sugiriendo que el SPL se relaciona con cambios en la biomecánica cornea, independientemente de la edad y del IAH.

En el cuarto estudio, los pacientes con SPL presentaron unos cambios significativos a nivel del epitelio conjuntival tras compararlos con pacientes sin SPL. En la bibliografía previamente publicada, no hemos encontrado estudios en los que se determinen los cambios citológicos de los pacientes con SPL comparándolos con pacientes controles. Un trabajo previo de Medel et al (89) estaba basado en el estudio de 16 pacientes (incluyendo 26 ojos) con SPL, en los cuales se les realizaba una citología de impresión conjuntival antes y después del tratamiento quirúrgico del SPL. Sus resultados mostraron una mejoría de los índices citológicos tras la cirugía, pero no incluyeron en el estudio pacientes sin SPL. El presente estudio representa el mayor tamaño muestral de pacientes con SPL en los que se les ha realizado una citología de impresión conjuntival.

Muchas patologías, como la dermatitis atópica, el pemfigoide cicatricial, el síndrome de Steve-Johnson, causticaciones, ojo seco y tracoma, han sido asociadas con un aumento de la metaplasia escamosa y una disminución en el número de células caliciformes (90). En el estudio que presentamos, se ofrecen unos datos objetivos que apoyan que las condiciones de hiperlaxitud palpebral causan una condición clínica caracterizada por cambios crónicos a nivel del epitelio conjuntival como son la pérdida de células caliciformes y la metaplasia escamosa.

Como resultado de la pérdida de células caliciformes y de la pérdida de diferenciación epitelial que presentan los pacientes con SPL, la película lagrimal se presentaría inestable, secundaria a la reducción de la capa de mucina. En ausencia

de mucina, las células epiteliales corneales son hidrofóbicas no pudiendo ser humedecidas por la capa acuosa de la lágrima (91). La reducción de las células caliciformes con contenido de mucina identificado con la tinción de PAS, se ha asociado con el síndrome del ojo seco y la inflamación de la superficie ocular. La metaplasia escamosa es el resultado de un proceso de diferenciación anormal epitelial debido a una transición patológica desde un epitelio no-queratinizado (secretor o no secretor) como el epitelio conjuntival, a un epitelio no-secretor queratinizado; esta metaplasia escamosa se ha asociado a la irritación crónica (92) como ocurre en los pacientes con SPL.

Este estudio muestra las alteraciones conjuntivales en los pacientes con SPL asumiendo que las causas que las producen son múltiples, e incluyen el trauma mecánico que puede ocurrir con la eversión nocturna, la disfunción de la lágrima y de las glándulas de Meibomio, la pobre aposición palpebral, y el daño a nivel de la piel palpebral (90,93). Algunos pacientes notan que cuando duermen el párpado superior se evierte y roza contra la almohada pudiendo provocar alteraciones corneales como queratopatía superficial o úlceras corneales así como un importante disconfort ocular. La disfunción de las glándulas de Meibomio causa un ojo seco evaporativo debido a la hiposecreción de lípidos en la lágrima y una desestabilizacón de la película lagrimal; esta inestabilidad es responsable de los síntomas de ojo seco (94-96). La piel palpebral de los pacientes con SPL de forma característica presenta un aumento en la temperatura, con un mayor grado de evaporación de la lágrima e hiperpigmentación (91). En nuestra serie, los pacientes con SPL eran principalmente varones con un alto IMC, tal y como se describió el SPL en sus inicios. El SPL asociado a un alto IMC y al SAHS, debería sospecharse en todo paciente obeso con síntomas de disconfort ocular crónicos (97). La hipoxia durante el sueño puede no sólo causar la laxitud palpebral sino que puede provocar daño en la piel palpebral debido a una lesión asociada a la isquemia-reperfusión secundaria al SAHS. Como resultado, esta piel resultaría crónicamente inflamada, con temperatura más elevada y con una pérdida de las barreras naturales contra la evaporación de la lágrima.

En los resultados presentados en este estudio, tras ajustar a la edad y al IMC, los grados de metaplasia y de clasificación de Nelson fueron significativamente más altos en los pacientes con SPL que en los pacientes controles; esto sugiere que en el

SPL induce unos cambios significativos en el epitelio conjuntival objetivados en la citología de impresión, caracterizados por un aumento de la metaplasia y una disminución de las células caliciformes, independientemente de la edad y del IMC.

En muchos pacientes con SPL los síntomas oculares son resistentes al tratamiento médico. En este estudio observamos que el SPL está asociado a cambios significativos crónicos en el epitelio conjuntival. Por lo tanto, proponemos la citología de impresión conjuntival como una herramienta útil para cuantificar y monitorizar los cambios en la superficie ocular en los pacientes con SPL. La citología de impresión puede contribuir a la investigación de la patogénesis del SPL así como a su seguimiento y tratamiento.

CONCLUSIONES

Esta tesis doctoral se ha planteado para profundizar en la asociación entre la patología ocular y el SAHS, centrándonos en el SPL y el glaucoma.

Las conclusiones más relevantes de los estudios presentados son:

1. La hiperlaxitud palpebral se asocia al SAHS, sugiriendo que el SAHS puede ser un factor de riesgo independiente para la hiperlaxitud palpebral.

2. El SPL está estrechamente asociado al SAHS con una presencia de SAHS entre los pacientes con SPL del 85%, la mayoría de ellos con SAHS severo. La prevalencia de SAHS entre los pacientes con SPL es muy alta, pero no lo es tanto la prevalencia de SPL entre la población general con SAHS (16%).

3. Los pacientes con diagnóstico de SPL deben ser interrogados de rutina sobre síntomas relacionados con el SAHS y considerar su derivación al correspondiente especialista de sueño. De modo, que los oftalmólogos pueden ser los primeros profesionales que remitan a los pacientes con SPL a la correspondiente Unidad de Sueño para descartar SAHS.

4. El SPL puede ser un factor predictivo para la presencia de glaucoma entre los pacientes con SAHS. Dada la alta prevalencia de glaucoma en los pacientes con SAHS y SPL observada en nuestro estudio, recomendamos descartar glaucoma en todos los pacientes con SPL y SAHS.

5. El SPL se asocia a unos cambios significativos a nivel de la biomecánica corneal caracterizados por una histéresis corneal más baja, sugiriendo que cambios estructurales adicionales pueden estar presentes en el SPL.

6. La citología de impresión conjuntival es un método objetivo para evaluar los cambios en la superficie ocular de los pacientes con SPL. Los pacientes con SPL presentan unos cambios significativos en el epitelio conjuntival

caracterizados por una pérdida de células caliciformes y un aumento de la metaplasia escamosa.

BIBLIOGRAFÍA

1. Duran J, Esnaola S, Rubio R, et al. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163:685-689.
2. Young T, Palta M, Dempsey J, et al. The occurrence of sleep disorders breathing among middle aged adults. N Engl J Med 1993;328:1230-1236.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Resp Crit Care Med 2002;165:1217-39.
4. Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. Standards of Practice Committee of the American Sleep Disorders Association. Sleep 1994;17:372-377.
5. Douglas N, Thomas S, Jan M. Clinical value of polysomnography. Lancet 1992;339:347-350.
6. Kingshott R, Engleman H, Deary I, et al. Does arousal frequency predict daytime function? Eur Respir J 1998;12:1264-1270.
7. Flemons W, Douglas N, Kuna S, et al. Access to diagnosis and treatment of patients with suspected sleep apnea. Am J Respir Crit Care Med 2004;169:668-672.
8. Masa J, Montserrat J, Duran J. Diagnostic access for sleep apnea in Spain. Am J Respir Crit Care Med 2004;170:195-196.
9. Culbertson WW, Ostler HB. The floppy eyelid syndrome. Am J Ophthalmol 1981;92:568–575.
10. Robert PY, Adenis JP, Tapie P, et al. Eyelid hyperlaxity and obstructive sleep apnea (O.S.A) syndrome. Eur J Ophthalmol 1997;7:211–215.
11. Monjon DS, Hess C, Goldblum D, et al. High prevalence of glaucoma in patients with sleep apnea syndrome. Ophthalmology 1999;106:1009–1012.

12. Geyer O, Cohen N, Segev E, et al. The prevalence of glaucoma in patients with sleep apnea syndrome: same as in the general population. Am J Ophthalmol 2003;136:1093–1096.
13. Sergi M, Salermo DE, Rizzi M, et al. Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients. J Glaucoma 2007;16:42–46.
14. Lin PW, Friedman M, Lin HC, et al. Normal tension glaucoma in patients with sleep apnea/hypopnea syndrome. J Glaucoma 2011;20:553–558.
15. Chambe J, Laib S, Hubbard J, et al. Floppy eyelid syndrome is associated with obstructive sleep apnoea: a prospective study on 127 patients. J Sleep Res 2012;21:308–315.
16. Kadyan A, Asghar J, Dowson L, et al. Ocular findings in sleep apnoea patients using continuous positive airway pressure. Eye 2010;24:843–850.
17. Pihlblad MS, Schaefer DP. Eyelid laxity, obesity, and obstructive sleep apnea in keratoconus. Cornea 2013;32:1232-6.
18. Mojon DS, Mathis J, Zulauf M, et al. Optic neuropathy associated with sleep apnea syndrome. Ophthalmology 1998;105:874–877.
19. Palombi K, Renard E, Levy P, et al. Nonarteritic anterior ischemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. Br J Ophthalmol 2006;90:879-82.
20. Bucci FA Jr, Krohel GB. Optic nerve swelling secondary to the obstructive sleep apnea syndrome. Am J Ophthalmol 1988;105:428–430.
21. Yavas GF; Küsbeci T, Kasikci M, et al. Obstructive sleep apnea in patients with central serous chorioretinopathy. Curr Eye Res 2014;39:88-92.
22. Leroux les Jardins G, Glacet-Bernard A, Lasry S, et al. Retinal vein occlusion and obstructive sleep apnoea syndrome. J Fr Ophthalmol 2009;32:420-4.
23. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med 2002;165:934-939.
24. Alonso-Fernández A, García-Río F, Arias M, et al. Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial. Thorax 2009;64:581-586.
25. Somers V, Dyken M, Clary M, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897-1904.

26. Somers V, Mark A, Zavala D, et al. Contrasting effects of hipoxia and hipercapnia on ventilation and sympathetic activity in humans. J Appl Physiol 1989;67:2101-2106.
27. Rubinstein I. Nasal inflammation in patients with obstructive sleep apnea. The Laryngoscope 1995;105:175-177.
28. Kohler M, Stradling J. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7:677-685.
29. Phillips C, McEwen B, More-Kopp MC, et al. Effects of continuous positive airway pressure on coagulability in obstructive sleep apnoea: a randomised, placebo-controlled crossover study. Thorax 2012;67:639-644.
30. Känel V, Loredo J, Ancoli-Israel S, et al. Association between sleep apnea severity and blood coagulability: Treatment effects of nasal continuous positive airway pressure. Sleep Breath 2006;10:139-146.
31. Robinson G, Pepperell J, Segal H, et al. Circulating cardiovascular risk factors in obstructive sleep apnea: data from randomised controlled trials. Thorax 2004;59:777-782.
32. Toukh M, Pereira E, Falcon B, et al. CPAP reduces hypercoagulability as assessed by thromboelastography, in severe obstructive sleep apnoea. Respir Physiol Neurobiol 2012;183:218-223.
33. Budhiraja R, Parthasarathy S, Quan S. Endothelial dysfunction in obstructive sleep apnea. J Clin Sleep Med 2007;3:409-415.
34. Shamsuzzaman A, Gersh B, Somers V. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290-1906-1194.
35. Sugita Y, lijima S, Teshima Y, et al. Marked episodic elevation of cerebrospinal fluid pressure during nocturnal sleep in patients with sleep apnea hypersomnia syndrome. Electroencephalogr Clin Neurophysiol 1985;60:214-19.
36. Grover D. Obstructive sleep apnea and ocular disorders. Curr Opin Ophthamol 2010;21:454-8.
37. Paciuc M, Mier ME. A woman with the floppy eyelid syndrome. Am J Ophthalmol 1982;93(2):255-6.
38. Eiferman RA, Gossman MD, O'Neill K, Douglas CH. Floppy eyelid syndrome in a child. Am J Ophthalmol 1990;109:356-7.

39. Parunovic A. Floppy eyelid syndrome. Br J Ophthalmol 1983;67:264-6.
40. Tzong-Shyue D, Di Pascuale M, Gao Y, et al. Tear film dynamics in floppy eyelid syndrome. Invest ophthalmol Vis Sci 2005;46:1188-1194.
41. Valenzuela AA, Sullivan T. Medial upper eyelid shortening to correct medial eyelid laxity in floppy eyelid syndrome: a new surgical approach. Ophthalmic Plast Reconstr Surg 2005;21:259-63.
42. Langford JD, Linberg JV. A new physical finding in floppy eyelid syndrome. Ophthalmology 1998;105:165-9.
43. Liu DT, Di Pascuale MA, Sawai J, et al. Tear film dynamics in floppy eyelid syndrome. Invest Ophthalmol Vis Sci 2005;46:1188-94.
44. Culberston WW, Tseng SC. Corneal disorders in floppy eyelid syndrome. Cornea 1994;13(1):33-42.
45. Rossiter JD, Ellingham R, Hakin KN, Twomey JM. Corneal melt and perforation secondary to floppy eyelid syndrome in the presence of rheumatoid arthritis. Br J Ophthalmol 2002;86:483.
46. Donnenfeld ED, Perry HD, Gibralter RP, et al. Keratoconus associated with floppy eyelid syndrome. Ophthalmology 1991;98:1674-8.
47. McMonnies XW. The evidentiary significance of case reports: eye rubbing and keratoconus. Optom Vis Sci 2008;85:262-9.
48. Gonnering RS, Sonneland PR. Meibomian gland dysfunction in floppy eyelid syndrome. Ophthal Plast Reconstr Surg 1987;3:99-103.
49. Goldberg RA, Coden DJ, Hornblass A, Mitchell JP. Floppy eyelid syndrome associated with marked lower eyelid ectropion. Am J Ophthalmol 1998;108:610-2.
50. Woog JJ. Obstructive sleep apnea and the floppy eyelid syndrome. Am J Ophthalmol 1990;110:314-5.
51. Mojon DS, Godlblum D, Fleichhauer J, et al. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. Ophthalmology 1999;106:1182-5.
52. Karger RA, White WA, Park WC, et al. Prevalence of floppy eyelid syndrome in obstructive sleep apnea-hypopnea syndrome. Ophthalmology 2006;113:1669-74.
53. McNab AA. Floppy eyelid syndrome and obstructive sleep apnea. Ophthal Plast Reconstr Surg 1997;13:98-114.

54. Ezra DG, Beaconsfield M, Sira M, et al. The associations of floppy eyelid syndrome: a case control study. Ophthalmology 2010;117:831-8.
55. McNab AA. Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnea. Clin Experiment Ophthalmol 2000;28:125-6.
56. Ezra D, Ellis J, Gaughan C, et al. Changes in tarsal plate fibrillar collagens and elastic phenotype in floppy eyelid syndrome. Clin Exp Ophthalmol 2011;39:564-71.
57. Ezra DG, Ellis JS, Beaconsfiled M, et al. Changes in fibroblast mechanical set point and mechanosensitivity: an adaptative response to mechanical stress in floppy eyelid syndrome. IOVS 2010;51:3853-63.
58. Taban M, Perry JD. Plasma leptin levels in patients with floppy eyelid syndrome. Ophthal Plast Reconstr Surg 2006;22:375-7.
59. Schlotzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, et al. The pathogenesis of floppy eyelid syndrome: involvement of matrix metalloproteinases in elastic fiber degradation. Ophthalmology 2005;112:694-704.
60. Charles JM. Wake up to floppy eyelid syndrome. Br J Ophthalmol 2013;97:1363-1364.
61. Series F, Chakir J, Boivin D. Influence of weight and sleep apnea status on immunologic and structural features of the uvula. Am J Respir Crit Care Med 2004;170:541–546.
62. McNab AA. The eye and sleep. Clin Experiment Ophthalmol 2005;33:117-25.
63. Bonomi L, Marchini G, Marrafa M, et al. Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. Ophthalmology 1998;105:209-215.
64. Dielemans I, Vingerling JR, Wolfs RCW, et al. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. Ophthalmology 1994;101:1851-1855.
65. Kargi SH, Altin R, Koksal M, et al. Retinal nerve fibre layer measurements are reduced in patients with obstructive sleep apnoea syndrome. Eye (Lond) 2005 May;19(5):575-9.

66. Karakucuk S, Goktas S, Aksu M, et al. Ocular blood flow in patients with obstructive sleep apnea syndrome (OSAS). Graefes Arch Clin Exp Ophthalmol 2008;246:129-34.
67. Kiekens S, Veva De Groot, Coeckelbergh T, et al. Continuous positive airway pressure therapy is associated with an increase in intraocular pressure in obstructive sleep apnea. Invest Ophthalmol Vis Sci 2008;49:934-40.
68. Waller EA, Bendel RE, Kaplan J. Sleep disorders and the eye. Mayo Clin Proc 2008;83:1251-1261.
69. Iyengar SS, Khan JA. Quantifying upper eyelid laxity in symptomatic floppy eyelid syndrome by measurement of anterior eyelid distraction. Ophthal Plast Reconstr Surg 2007;23:255.
70. Egbert PR; Lauber S, Maurice DM. A simple conjunctival biopsy. Am J Ophtahlmol 1977;84:798-801.
71. Nelson JD, Wright JC. Conjunctival goblet cell densities in ocular surface disease. Arch Ophthalmol 1984;102:1049-1051.
72. Iber C, Ancoli-Israel, Chesson A, et al. The American Academy of Sleep Medicine manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st edn. Westchester, IL: Academy of Sleep Medicine, 2007.
73. Fowler AM, Dutton JJ. Floppy eyelid syndrome as a subset of lax eyelid condition: relationships and clinical relevance (an ASOPRS Thesis). Ophthal Plast Reconst Surg 2010;26:195-204.
74. Netland PA, Sugrue SP, Albert DM, et al. Histopathologic features of the floppy eyelid syndrome. Involvement of tarsal elastin. Ophthalmology 1994;101:174-81.
75. Abdal H, Pizzimenti JJ, Purvis CC. The eye in sleep apnea syndrome. Sleep Med 2006;7:107-15.
76. Mc Naab A. The eye and sleep. Sleep Med Rev 2007;11:269-72.
77. Bengtsson B Heijl A. A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. J Glaucoma 2005;14:135-138.
78. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. Surv Ophthalmol 2008;53(suppl 1):S3-S10.

79. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg 2005;31:156-62.
80. Kamiya K, Hagishima M, Fujimura F, Shimizu K. Factors affecting corneal hysteresis in normal eyes. Graefes Arch Clin Exp Ophthalmol 2008;246:1491-4.
81. Kida T, Liu JH, Weinreb RN. Effects of aging on corneal biomechanical properties and their impact in 24-hour measurement of intraocular pressure. Am J Ophthalmol 2008;146:567-72.
82. Congdon N, Broman A, Bandeen-Roche K, Groer D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol 2006;141:868-875.
83. Kaushik S, Pandy SS, Banger A, Aggarwal K, Gupta A. Relationship between corneal biomechanical properties, central corneal thickness, and intraocular pressure across the spectrum of glaucoma. Am J Ophthalmol 2012;153(5):840-849.
84. Morita T, Shoji N, Kamiya K, Fujimura K, Shimizu K. Corneal biomechanical properties in normal-tension glaucoma. Acta Ophthalmol 2012;90(1):48-53.
85. Fontes B, Ambrósio R, Jardim D, Velarde GC, Nosé W. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. Ophthalmology 2010;117:673-679.
86. Hosseini A, Abolbashari F, Niyazmand H, Sedaghat MR. Efficacy of corneal tomography parameters and biomechanical characteristic in keratoconus detection. Cont Lens Anterior Eye 2014;37(1):26-30.
87. Johnson RD, Nguyen MT, Lee N, Hamilton DR. Corneal biomechanical properties in normal, forme fruste keratoconus, and manifest keratoconus after statistical correction for potentially confounding factors. Cornea 2011 May;30(5):516-23.
88. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal biomechanical properties and their variation with age. Curr Eye Res 2007;32:11-19

89. Medel R, Alonso T, Vela JI, et al. Conjunctival cytology in floppy eyelid syndrome: objective assessment of the outcome of surgery. Br J Ophthalmol 2009;93:513-517.
90. Calonge M, Yolanda D, Sáez V, et al. Impression cytology of the ocular surface: a review. Exp Eye Res 2004;78:457-72.
91. Karalezli A, Borazan M, Altinors D, et al. Conjunctival impression cytology, ocular surface, and tear-film changes in patients treated with systemic isotretinoin. Cornea 2009;28:46-50.
92. Dos Santos F, Domingues E, de Nadai J, et al. Impression cytology findings in bullous keratopathy. Br J Ophthalmol 2010;94:773-776.
93. Tzong-Shye D, Di Pascuale M, Gao Y, et al. Tear film dynamics in floppy eyelid syndrome. Invest Ophthalmol Vis Sci 2005:46:1188-1194.
94. Lemp M, Bron A, Baudiouin C, et al. Tear Osmolarity in the diagnose and management of dry eye disease. Am J Ophthalmol 2011;151(5):792-798.
95. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. Arch Ophthalmol 1995;113:1266-70.
96. Lee SH, Tseng SC. Rose Bengal staining and cytologic characteristics associated with lipid tear deficiency. Am J Ophthalmol 1997;124:736-50.
97. Pham TT, Perry JD. Floppy eyelid syndrome. Curr Opin Ophthalmol 2007;18(5):430.

PARTE II

APÉNDICES

La doctoranda MªJesús Muniesa Royo es licenciada en Medicina y Cirugía (Universitat de Lleida, 2000). Realizó la formación de Médico Interno Residente (MIR) de Oftalmología en el Hospital Universitario de La Princesa de Madrid, 2005. Desde hace 9 años trabaja como Facultativa Especialista de Oftalmología en el Hospital Universitario Arnau de Vilanova de Lleida (HUAV) como responsable de la Sección de Glaucoma.

Desde hace 5 años, forma parte del grupo de investigación de l'Institut de Recerca Biomèdica de Lleida (Fundación Dr. Pifarré) liderado por el Dr. Barbé; grupo investigador con alta experiencia científico-técnica en el campo de los trastornos respiratorios durante el sueño. La doctoranda en 2009 inició su trayectoria investigadora centrándose en las patologías oculares relacionadas con el síndrome de apnea-hipoapnea del sueño, combinando esta actividad investigadora con la actividad clínica asistencial. En este proyecto han participado el Servicio de Oftalmología del HUAV, Servicio de Neumología y Unidad del Sueño del HUAV y Hospital Santa María de Lleida y el Servicio de Anatomía Patológica del HUAV.

Los principales resultados de esta línea de investigación se han mostrado en la presente Tesis.

Este proyecto de investigación sobre patología ocular y el síndrome de apnea-hipoapnea del sueño ha recibido financiación de distintas becas en las que la doctoranda ha sido colaboradora: Instituto de Salud Carlos III (FIS PS09/02224); SOCAP 2009; SEPAR 2011, IRBLleida 2012.

Durante este tiempo la doctoranda ha presentado comunicaciones en congresos nacionales e internacionales, destacando:

- El síndrome del párpado laxo como indicador de mayor probabilidad de glaucoma en pacientes con el síndrome de apnea del sueño. SECOIR 2013. Premio a la mejor comunicación en su área.

- Estudio de la superficie ocular mediante citología de impresión conjuntival . ASETCIRC 2011. Premio a la mejor comunicación en el área de superficie ocular.

- El síndrome del párpado laxo y el síndrome de apnea del sueño: estudio de prevalencia. Congreso de la Sociedad Catalana de Oftalmología 2010. Premio a la mejor comunicación oral.

La producción científica de la doctoranda en la línea de investigación propuesta en esta Tesis, se ve también reflejada en los siguientes trabajos y referencias:

Trabajos y artículos:

- Muniesa MJ, March A, , Huerva V, Sánchez de la Torre M, Barbé F. Ponencia Oficial SECOIR 2014. Capítulo 19. Biomecánica corneal y otras patologías oculares: Biomecánica corneal en el síndrome del párpado laxo.

- Muniesa MJ, Traveset A, Ezpeleta J. Síndrome del párpado laxo. Revista de casos clínicos 4. Angelini. Mayo 2014.

- Huerva V, Muniesa MJ, Ascaso, FJ. Floppy eyelid syndrome in obstructive sleep apnea. Sleep Medicine 2014 Mar 13 (Epub ahead of print).

- Huerva V, Sánchez C, Muniesa MJ, Ruiz A. Lacrimal surgery in patients with obstructive sleep apnea. Sleep Medicine 2011;12:1046-7.

- Huerva V, Muniesa MJ. Síndrome de Floppy palpebral y su relación con el síndrome de apnea obstructiva del sueño. Arch Soc Esp Oftalmol 2007;82: 335-336.

Referencias al trabajo de investigación presentado:

- Charles JM. Wake up to floppy eyelid syndrome. Br J Ophthalmol 2013;97:1363-1364. Editorial.

- Michelle Dalton. Sleep disorders linked to glaucoma, floppy eyelid syndrome. EyeWorld. The Newsmagazine of the American Society of Cataract and Refractive Surgery. October 2013.

Wake up to floppy eyelid syndrome

Charles J M Diaper

Floppy eyelid syndrome (FES) encompasses a group of disorders involving easily everting eyelids in association with a thickened elastic tarsal plate. First described by Cultberston and Ostler over 30 years ago,[1] a patient's symptoms are those of ocular irritation, often unilateral and non-specific. The difficulty patients can have describing their ocular problems and the overlap with other causes of ocular irritation mean the condition can often be overlooked or dismissed as trivial in a primary care setting or when presenting to the hospital eye service. Patients are often obese with eyelids which easily evert with minimal traction. Chronic papillary conjunctivitis and lash ptosis may be visible on the affected side.[2]

Since first being described, FES has been found to be associated with a number of other diseases. The strongest associations identified are with obstructive sleep apnoea (OSA)[3–7] and keratoconus.[3] In this issue of the *BJO* Muniesa *et al*[8] provide further supportive evidence by way of a masked cross-sectional study, strengthening the link between OSA and FES. Increased lid laxity occurs with increasing severity of OSA, the prevalence of frank FES ranging from 2.3% to 31.5%;[6 7] these results are confounded by obesity. Studies have shown FES to be strongly associated with severe OSA[3 5–8] but the association is not reciprocated.[7]

OSA is a potentially serious condition with the risk of significant morbidity. Periods of recurrent apnoea occur during sleep due to airway collapse. This may happen hundreds of times a night lasting 10–30 s.[9] It is characterised by loud snoring, daytime sleepiness and episodes of apnoea; other features include waking with dry or sore mouth, morning headache, nocturia and insomnia.[9] There are associated changes in heart rate, oxygen saturation and the EEG. Sleep apnoea has consequences for general health over and above those of obesity; increasing the risk of cerebrovascular and cardiac disease.[10]

Sleep apnoea poses an increasingly significant health problem involving adults and children, affecting approximately 24% of men and 9% of women.[10] Obesity is a predisposing factor[10] and this is an increasing worldwide problem.[11] Affected patients have an anatomical deficiency of the upper airway with increased soft tissue volume.[12] The long axis of the oval pharyngeal opening is in the sagittal plane as opposed to the coronal plane in normal subjects. This may predispose to mechanical collapse.

Can a common pathophysiology play a role in linking these?

Studies have shown that the pathological tarsal plate changes are not those suggestive of a primary disorder of collagen or elastic fibres,[13–16] where the tissue tends to be stiff with poor mobility. Instead the changes in FES affect the extracellular matrix, collagen fibres and elastic fibres and are thought to be due to the response to mechanical stress. These may represent a local protective mechanism in response to repeated mechanical trauma to local tissues with the resultant chronic disease state. In OSA, possibly due to sleep position there is repeated mechanical pressure on the eyelids leading to eversion and trauma. The severity of FES correlates well with that of OSA, those with the most severe OSA having the greatest amount of lid laxity.[4 8]

Mechanical stress as a pathological mechanism links the high association of FES with keratoconus; well known for its relationship with eye rubbing. This may give a refractive cause, rather than an ocular surface reason, for decreased vision in patients with FES.[3]

Similar changes may occur in the soft tissues of the airways with repeated mechanical trauma due to their collapse in the prone sleeping position. These changes may further exacerbate the problem of OSA.

FES may be treated conservatively with lubrication and taping or shielding of the eyelid from the inducing trauma. There are conflicting reports as to whether management of the underlying OSA with continuous positive airways pressure is effective in the treatment of FES.[7 17] Lid laxity can be treated by a number of lid tightening procedures[18] with one recent study of long-term outcomes identifying recurrence rates with lateral canthal strip, medial and lateral canthal plication and full thickness wedge excision of 25.6%, 47% and 60.6% respectively.[19] In this series of 78 patients with FES, 20 had OSA. It was felt that the relatively high recurrence rate was due to the duration of follow-up, with most previous studies lacking any significant follow-up period. It was not speculated how the treatment of OSA influenced the outcome of the FES; a study into this now may well be unethical.[7]

OSA is treated with behavioural modifications and continuous positive airways pressure while sleeping. The behavioural modifications involve weight loss, increased physical activity and avoidance of alcohol and sedatives before bed. Second-line surgeries of various levels of invasiveness are available with the aim of decreasing airway obstruction.[20]

OSA is associated with other ocular conditions. These include glaucoma,[12] non-arteritic anterior ischaemic neuropathy, papilloedema, central serous retinopathy and retinal vein occlusion. Glaucoma may be related to the nocturnal apnoea or vascular deregulation that is well recognised in OSA. Vascular deregulation may also play a link in non-arteritic anterior ischaemic optic neuropathy and retinal vein occlusion.[21 22] Apnoea causing nocturnal hypoxaemia and hypercapnia, resulting in cerebral vasodilation, may be the link with papilloedema. A proportion of patients initially thought to have idiopathic intracranial hypertension, a condition often also associated with obesity, may turn out to have OSA and therefore a history of daytime somnolence should be sought.[23] Raised catecholamine levels are seen in patients with OSA and may predispose them to central serous retinopathy.[9]

Obesity is a significant risk factor for FES and OSA. It is a worldwide problem of preventable morbidity and mortality with the WHO labelling it an 'epidemic'.[11] In Scotland 26.8% of the population are obese (body mass index>30) with only the USA and Mexico ranked higher in the Organisation of Economic Co-operation and Development countries and estimated to raise to 40% by 2030.[24] To this end there is Scottish intercollegiate Guidelines Network Guidance[25] for healthcare workers to help address this problem.

Ophthalmologists should be aware of the systemic health problems posed by obesity as these can manifest as common conditions seen in the ophthalmology clinic, for example, diabetes, glaucoma and vein occlusion. Ophthalmologists should not avoid or shy away from initiating discussion with patients in regard to their weight management.

Ophthalmologists should be aware of the association between FES and OSA; an appropriate referral to a sleep physician could be life saving.

Correspondence to Mr Charles J M Diaper, Ophthalmology Department, Southern General Hospital, 1345 Govan Road, Glasgow GS1 4TF, UK; charles.diaper@ggc.scot.nhs.uk

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Diaper CJM. *Br J Ophthalmol* 2013;**97**:1363–1364.

▶ http://dx.doi.org/10.1136/bjophthalmol-2012-303051

Br J Ophthalmol 2013;**97**:1363–1364.
doi:10.1136/bjophthalmol-2013-303416

REFERENCES

1 Culbertson WW, Ostler HB. The floppy eyelid syndrome. *Am J Ophthalmol* 1981;92:568–75.
2 Langford JD, Linberg JV. A new physcial finding in floppy eyelid syndrome. *Ophthalmology* 1988;105:165–9.
3 Ezra DG, Beaconsfield M, Sira M, *et al*. The associations of Floopy eyelid syndrome: a case control study. *Ophthalmology* 2010;117:831–8.
4 Chambe J, Laib S, Hubbard J, *et al*. Floppy eyelid is associated with obstructive sleep apnoea: a prospective study on 127 patients. *J Sleep Res* 2012;21:308–15.
5 McNab AA. The eye and sleep apnea. *Sleep Med Rev* 2007;11:269–76.
6 Kadyan A, Asgher J, Dowson L, *et al*. Ocular findings in sleep apnoea patients using continuous positive airway pressure. *Eye* 2010;24:843–50.
7 Karger RA, White WA, Park W, *et al*. Prevalence of Floopy eyelid syndrome in obstructive sleep apnea-hypopnea syndrome. *Ophthalmology* 2006;113:1669–74.
8 Muniesa MJ, Huerva V, Torre MS, *et al*. *BJO* 2013; in press this volume.
9 Grover D. Obstructive sleep apnea and ocular disorders. *Curr Opin Ophthalmol* 2010;21:454–8.
10 Young T, Palta M, Dempsey J, *et al*. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–5.
11 WHO. *Obesity: preventing and managing the global epidemic*. Geneva: WHO, 2000.
12 Kargi SH, Altin R, Koksal M, *et al*. Retinal nerve fibre layer measurements are reduced in patients with obstructive sleep apnoea syndrome. *Eye (London)* 2005;19:575–9.
13 Ezra D, Ellis J, Gaughan C, *et al*. Changes in tarsal plate fibrillar collagens and elastic phenotype in floppy eyelid syndrome. *Clin Exp Ophthalmol* 2011;39:564–71.
14 Ezra DG, Ellis JS, Beaconsfiled M, *et al*. Changes in fribroblast mechanical set point and mechanosensitivity: an adaptive response to mechanical stress in floppy eyelid syndrome. *IOVS* 2010;51:3853–63.
15 Taban M, Taban M, Perry JD. Plasma leptin levels in patients with floppy eyelid syndrome. *Ophthal Plast Reconstr Surg* 2006;22:375–7.
16 Schlotzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, *et al*. The pathogenesis of floppy eyelid syndrome: involvement of matrix metalloprotienases in elastic fiber degradation. *Ophthalmology* 2005;112:694–704.
17 McNab AA. Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnoea. *Clin Exp Ophthalmol* 2000;28:125–6.
18 Ezra DG, Beaconsfield M, Colins R. Floppy eyelid syndrome: stretching the limits. *Surv Ophthalmol* 2010;55:35–46.
19 Ezra DG, Beaconsfield M, Sira M, *et al*. Long-term outcomes of surgical approaches to the treatment of floppy eyelid syndrome. *Ophthalmology* 2010;117:839–46.
20 Mannarino MR, Fillippo FD, Pirro M. Obstructive sleep apnea syndrome. *Eur J Intern Med* 2012;23:586–93.
21 Palombi K, Renard E, Levy P, *et al*. Nonarteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. *Br J Ophthalmol* 2006;90:879–82.
22 Leroux les Jardins G, Glacet-Bernard A, Lasry S, *et al*. Retinal vein occlusion and obstructive sleep apnea syndrome. *J Fr Ophtalmol* 2009;32:420–4.
23 Sugita Y, Iijima S, Teshima Y, *et al*. Marked episodic elevation of cerebrospinal fluid pressure during nocturnal sleep in patients with sleep apnea hypersomnia syndrome. *Electroencephalogr Clin Neurophysiol* 1985;60:214–19.
24 Donnelley RR. Preventing overweight and obesity, Scottish Government. 2010. ISBN: 978-0-7559-8183-0.
25 SIGN 115: Management of Obesity, Scottish Intercollegiate Guidelines Network. ISBN 978 1 905813 61 2.

2014-8-25 13:20:25

Date published online: October 2013

GLAUCOMA

Sleep disorders linked to glaucoma, floppy eyelid syndrome

by Michelle Dalton EyeWorld Contributing Writer

A spate of new studies has rejuvenated the interest in the association between these disorders

An example of floppy eyelid syndrome
Source: Francis S. Mah, MD

Think sleeping disorders and ocular disorders are two completely separate occurrences? Maybe not, if three recently published articles[1-3] are any indication. Obstructive sleep apnea (OSA) has been associated with a variety of ocular disorders, from floppy eyelid syndrome (FES) to keratoconus to infectious keratitis to glaucoma.[3]

OSA and glaucoma

Chin-Chun Lin, MA, and colleagues used a national, population-based dataset in Taiwan to determine the risk and prevalence of open-angle glaucoma (OAG) among patients with OSA over the course of 5 years.[3] Ahmad A. Aref, MD, reported on nighttime events that might lead to the development or progression of glaucomatous optic neuropathy.[2] Patients with OSA "were independently associated with a 1.67 times increased risk of OAG diagnosis within the first 5 years after their diagnosis," Prof. Lin wrote. The group noted two theories on the relationship exist—one suggesting the increased IOP and "stretching of the lamina cribrosa is the reason for glaucoma," but that obesity (or at least an increased body mass index) is also thought to be related to direct damage of the optic nerve, and an overwhelming majority of patients with OSA are overweight. The second theory suggests hypoxia can cause direct damage to the optic nerve and that the recurrent hypopnea characteristic of OSA is partially responsible for optic nerve head perfusion, the group noted.

"There is certainly enough early evidence to suggest that OSA plays a role in the progression of glaucoma," said Dr. Aref, assistant professor of ophthalmology, Illinois Eye & Ear Infirmary, Department of Ophthalmology & Visual Sciences, University of Illinois at Chicago. He noted these kinds of large, retrospective cohort studies "have some methodological limitations. They rely on billing diagnoses that are subject to underdiagnosis"—both OSA and glaucoma fall into this category because of their slowly progressive and largely asymptomatic nature. Case-control studies, on the other hand, "are better designed with prospectively diagnosed individuals with glaucoma, OSA, or both," he said.

OSA and FES

A few theories on the causal relationship between OSA and FES exist. "It could be possible that the elastic fiber depletion described in FES and OSA could indicate some of the characteristics present in other ocular structures, such as lamina cribrosa or/and trabecular meshwork," said Mª Jesús Muniesa Royo, MD, Department of Ophthalmology, Hospital Universitari Arnau de Vilanova, Lleida, Spain. "These changes could increase the risk of glaucoma in OSA patients affected by FES. The hypothesis is that a subtle form of underlying generalized connective tissue alteration could be responsible for the relationship between OSA, glaucoma and FES."

In Dr. Royo's study,[2] the results suggested OSA could be a subset of lax eyelid conditions and once that laxity reaches a certain threshold, patients would be at risk for developing FES with inflammatory sequelae of the conjunctiva, cornea, and tear film.

"These changes could explain how OSA, eyelid hyperlaxity, and FES could be different manifestations of the same disease," Dr. Royo said. In fact, the study found among patients with FES, the prevalence of OSA was 85%, and most of the OSA was considered serious. "FES may be a predictive factor for the presence of glaucoma in patients with OSA."

If further studies support these new findings, Dr. Aref said "this relationship would have a profound clinical impact, as it would give ophthalmologists an objective sign to determine risk of glaucoma in association with OSA."

Take-home messages

Clinicians should consider "routine screening of newly diagnosed FES patients for symptoms of sleep apnea and consider referral to a sleep specialist," Dr. Royo said.

For patients who have glaucoma progression at pressure levels previously deemed to be adequate, "the clinician should seriously consider an underlying diagnosis of OSA potentially contributing to nocturnal optic nerve perfusion abnormalities and causing non-pressure, dependent disease progression," Dr. Aref said. At a minimum, he suggested clinicians question nighttime sleeping habits (snoring, apneic episodes). "There should be an extremely low threshold for OSA work-up in these circumstances as this disorder may not only impact glaucomatous progression, but may have serious general health consequences such as increased risk of cardiovascular and cerebrovascular events," he said.

References

1. Aref AA. What happens to glaucoma patients during sleep? Curr Opin Ophthalmol. 2013;24(2):162-6.
2. Muniesa MJ, Huerva V, Sanchez-de-la-Torre M, Martinez M, Jurjo C, Barbe F. The relationship between floppy eyelid syndrome and obstructive sleep apnoea. Br J Ophthalmol doi:10.1136/bjophthalmol-2012-303051 [online ahead of print].
3. Lin CC, Hu CC, Ho JD, Chiu HW, Lin HC. Obstructive sleep apnea and increased risk of glaucoma: A population-based matched-cohort study. Ophthalmology. 2013 Apr 16. pii: S0161-6420(13)00008-0. doi: 10.1016/ j.ophtha.2013.01.006 [Epub ahead of print].

***Editors' note**: The physicians have no financial interests related to this article.*

Contact information

Aref: aaref@uic.edu

Royo: +34 649 297 040, mariajesus.muniesa@gmail.com